



# SURGERY

A Monthly Journal Devoted to the Art  
and Science of Surgery

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# SURGERY

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## Original Communications

### THE PHYSIOLOGY, PATHOLOGY, AND CLINICAL SIGNIFICANCE OF EXPERIMENTAL CORONARY SINUS OBSTRUCTION\*

ITS RELATION TO CARDIAC SURGERY, CORONARY THROMBOSIS, AND NUTRITION OF THE HEART BY THEBESIAN VESSEL OR CORONARY SINUS BACKFLOW

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THOUGH much has been learned regarding the results of coronary artery occlusion, closure of any of the veins of the heart, or of the coronary sinus which drains the heart to a large extent has not been frequently noted or the concomitant pathologic and physiologic changes detailed. In the following clinical, pathologic, and physiologic study of such closure in animals enlightenment was desired on the following points:

1. With the advance of cardiac surgery the clinician requires data regarding effects subsequent to the occlusion of the cardiac venous system, while from an experimental viewpoint these data are also valuable, especially with regard to whether ligation of veins with arteries will complicate studies on coronary artery closure.

2. During the course of these studies, physiologic changes indicating the liberation in the heart of a vasodilatory and cardioinhibitory substance were noted frequently following occlusion of the coronary sinus. The phenomenon occurred after the sinus was closed, and the usual and largest return channel of venous blood thus blocked, if the thebesian vessels did not return enough blood from the heart wall directly to the heart cavities to prevent congestion and cyanosis of the left heart. Considerable attention is paid today to the so-called cardiac hormone and to similar substances extracted from striped and unstriped muscle as well as other tissues which have a vasodilatory

\*This work was done partially in Edinburgh through the kindness of the late Sir David Wilkie and at the Harvard Medical School under Professor E. C. Cutler, 1932-1935.

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action.<sup>1-10</sup> The heart proves excellent for a study of such effects and their possible application for the alleviation of occlusive states of the coronary vessels. Further, these physiologic changes were correlated with pathologic findings. One hoped these findings would be valuable in that they should be those found by others to be coexistent with venous occlusion accompanied by various degrees of circulatory stasis in different regions of the body.<sup>11, 12</sup> Here again the heart presented itself as an excellent site for the study of circulatory phenomena of this type, many of its responses being readily noted.

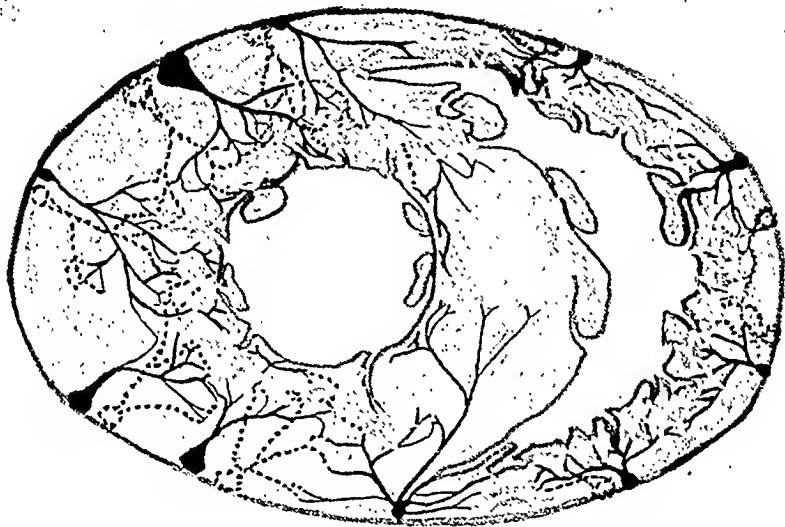


Fig. 1.—Diagrammatic representation of vessels of Vieussens and Thebesius (white) forming a network of vessels in connection with coronary arteries (black solid) and coronary veins (black dotted). The left coronary artery drains largely to the coronary sinus by its veins but has connections through the network with the left ventricular cavity. The right coronary artery drains largely to the cavities of the right auricle and ventricle through the network, little arterial blood returning to the right auricle by way of coronary veins.

3. It has been suggested that blood from the heart cavities may flow into the heart wall to nourish it adequately and minimize the effects of coronary artery closure. Such a flow is said to occur along the small vessels shown by Vieussens to connect the arteries, and by Thebesius to connect the veins, of the heart wall with the heart cavities.<sup>10, 13-17, 19, 20</sup> If this were true and if the heart could tolerate readily closure of the coronary sinus, dilatation of the venous channels should follow such closure and subsequent coronary artery ligation should have minimal effects. Other workers have suggested that in coronary artery closure blood may flow back from the right auricle into the coronary sinus and its tributaries to penetrate the heart wall and nourish it.<sup>13-15, 20, 21</sup> The physiologic data in support of this concept need additions to show whether such a flow would be likely to occur and how efficient it might be.

4. Last, our work included extensive electrocardiographic studies, correlated carefully with the other data, on the assumption that venous obstruction might present pictures different or capable of differentiation from arterial closure or might enhance our knowledge of the effects of cyanosis and myocardial death on conduction curves.

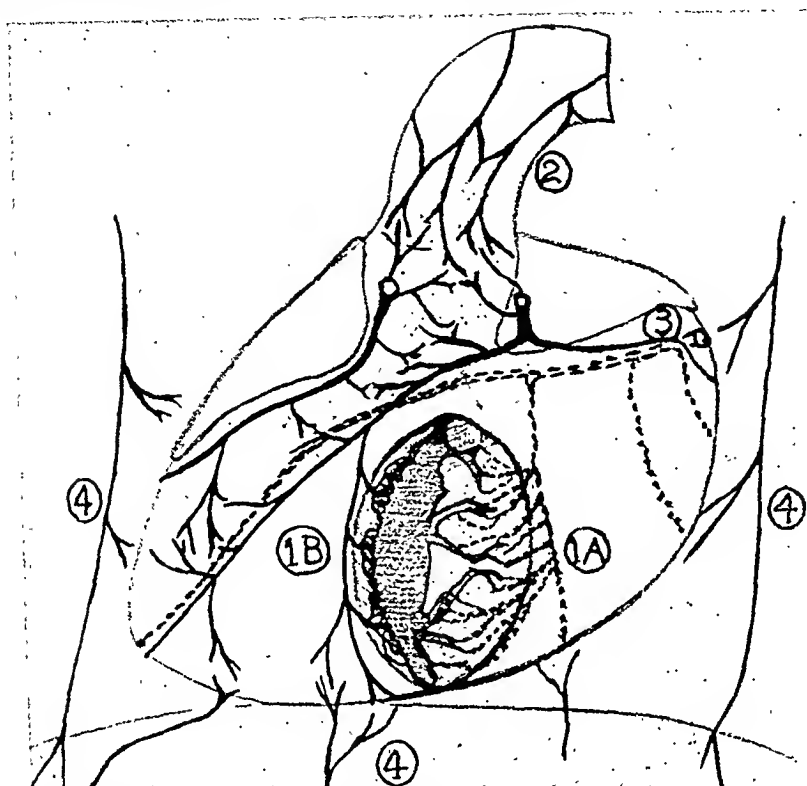


Fig. 2.—Diagrammatic representation of coronary arteries in relation to vessels of Vieussens (black solid) and coronary veins in relation to vessels of Thebesius (black dotted) and of supposed accessory modes of blood supply to the heart in coronary occlusion. 1A, coronary veins and vessels of Thebesius; 1B, coronary artery and vessels of Vieussens; 2, vasa vasorum of ascending limb of thoracic aorta; 3, coronary sinus; 4, pericardial, diaphragmatic, and other thoracic vessels by adhesions.

#### LITERATURE

The knowledge to date regarding these questions is summarized as follows:

*Anatomy.*—Vieussens and Thebesius, by injection experiments and dissections in a variety of hearts, demonstrated that small channels join the cavities of the heart with the arteries and the veins of the heart wall. It has since been demonstrated that these small vessels develop from embryonic sinusoidal channels which at first are only connected with the heart cavities, but later join the coronary arteries and veins. The size of the vessels must vary, and workers do not agree whether they are always capillary in size or whether they may have arteriolar and venular magnitude, or be even larger. They communicate very freely, however,

one with another, and with the intramural network of arteries and veins. Some attempt has been made to differentiate clearly the vessels of Vieussens, which are supposed to have to do only with the arterial side, from the vessels of Thebesius, said to be venous in character. Though anatomically vessels eventually may be associated more intimately with one or other side of the circulation, the physiologic concept is the more important and, as noted below, the whole system may functionally be grouped as one. Though clear-cut evidence is lacking, it is probable that the vessels of Vieussens and Thebesius are most numerous in the right heart, are quite numerous in the left ventricle, especially about the



Fig. 3.—Low-power photomicrograph of section of dog's ventricular wall, showing large blood sinuses running far into the wall, and almost to the epicardial surface, from the ventricular cavity.

apex, and are absent or rarely present in the left auricle. Such a distribution agrees with Thebesius' concept that the system is for rapid drainage of venous blood from the heart wall. This distribution also agrees with the fact that on the right side of the heart is found a thin and highly trabeculated wall, a short route necessary for the return of arterial blood to the right heart cavities, and a corresponding paucity of veins; while on the left side of the heart there is a thick ventricular wall and a definite and efficient venous system to carry the blood a relatively long distance to the right heart cavities<sup>13, 15, 17-24</sup> (Figs. 1-4).

The major veins of the right heart are about a half-dozen in number and usually enter separately into the right auricle. Several enter the sinus by way of the small cardiac vein or the right marginal vein. The veins of the left heart form a slightly variable but definite system. The veins accompanying the left coronary artery branches end in the coronary sinus, a structure 2 or 3 cm. long, which commences where the oblique vein of the left auricle and the left marginal vein join the great cardiac vein near the junction of the left auricular body with its appendage. It possesses a rather inadequate valve near its commencement and another, equally inadequate, may be seen as its termination at the right auricle.



Fig. 4.—Low-power photomicrograph of section of dog's left heart wall some weeks after the coronary sinus of the heart had been ligated. Arrows trace several dilated thebesian vessels from endocardium to outer part heart wall.

Pertinent variations in these arrangements are several cases where the sinus was not patent by reason of embryonic lesions or old inflammatory lesions, yet no evidence of detrimental clinical or pathologic changes was noted in the hearts. In another case an arteriovenous aneurysm between a small artery and the coronary sinus of an adult heart had produced merely a slight dilatation of the joined vessels.<sup>25-27</sup>

*Physiology.*—It may be fairly said that Thebesius' statement of the function of the vessels now named after him, and those also of the type described by Viessens, still holds good. The vessels connecting the intramural arteries and the veins with the heart cavities were said to act as an overflow system for more quickly emptying the heart wall in case of sudden hyperfunction of the heart. The venous drainage of the right heart wall is largely into the cavities of the right heart directly, some

blood being returned by the right heart veins and only a small fraction entering the coronary sinus by way of the right marginal or small cardiac vein. The left heart wall empties itself largely into the coronary sinus through its numerous veins. A small part of the venous blood probably enters the left ventricular cavity directly, while none likely returns from the left auricular wall to the left auricle directly but is discharged into the sinus and its veins. The average heart in this way drains over 60 per cent of its venous blood into the coronary sinus, so that the left ventricular wall must discharge considerably over this percentage of its blood by way of the coronary sinus. The discharge of blood is made during systole by the intramural pressure which, rising in this phase over the aortic pressure to shut off the coronary artery inflow, squeezes blood from the heart wall either into the heart cavities or into the coronary veins <sup>13-15, 17-19, 28-31</sup> (Figs. 1-5).

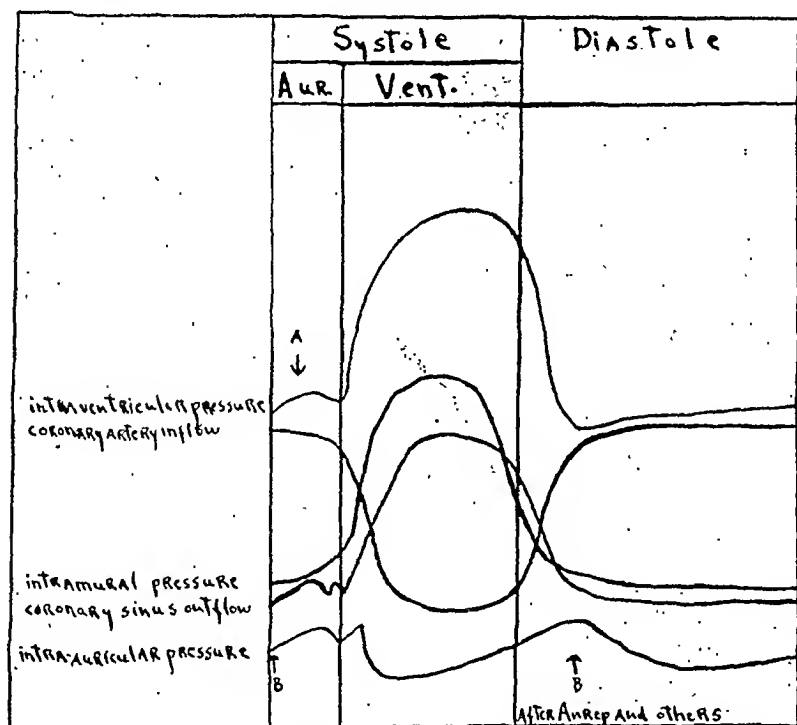


Fig. 5.—Composite diagram of various pressure curves relevant to nourishment of heart by thebesian backflow or coronary sinus backflow. A, Possible favorable point for thebesian backflow; B, possible favorable time for coronary sinus backflow.

In considering whether it is true that the thebesian vessels, as an accessory function, might nourish the heart wall in coronary occlusion by carrying blood into the wall from the heart cavities, the following physiologic data must be kept in mind. In ventricular systole there is a high intramural pressure which squeezes some of the blood from the heart wall through the valvelike slit openings of the thebesian vessels on

the endocardial surface of the heart wall. Throughout diastole not only does the coronary artery inflow distend the heart wall and tend to close the thebesian openings, but the intraventricular pressures are low. For a short period in auricular systole there is a diminution in coronary inflow and intraventricular pressures are rising, but there is already an increasing intramural pressure<sup>28-31</sup> (Figs. 1-5).

The nourishment of the heart by a coronary sinus backflow is perhaps favorable, on theoretical grounds, for two very brief periods: (1) during early auricular systole, just before coronary sinus outflow commences to increase and ventricular systole suddenly raises the coronary sinus and the intramural pressure; (2) during early diastole, when the auriculoventricular ring is moving upward, the intra-auricular pressure is being further increased by the inflow of blood during the time the auriculoventricular valves are closed, and intramural pressure and coronary sinus output are decreasing<sup>28-31</sup> (Figs. 1-5).

The experimental physiology bearing on the question of whether hearts suffering from occlusion of the coronary arteries can be nourished by the forcing of blood from the heart cavities into the heart wall is conveniently included here. Stella's experiments show that blood does not flow into the coronary arterial system from the heart cavities in the normal heart during acute experiments.<sup>32</sup> Robertson has shown in survival experiments on dogs that, after first dilating the thebesian vessels by ligation of the coronary sinus and then gradually occluding the coronary arteries completely, the heart is not nourished by a thebesian backflow but by the adhesions developed in the course of the experiment<sup>48</sup> (Fig. 4). However, various authors have shown that bacteria, and particles deposited in the heart cavities, find their way into the heart wall and the coronary venous system in some manner without first entering the main coronary arteries.<sup>20, 21</sup> Others have nourished hearts experimentally by coronary sinus or by intraventricular perfusion, and reports are found of human hearts maintaining their function though their coronary arteries were apparently occluded entirely or to a serious degree.<sup>13-15, 18, 19, 33-35</sup>

*Experimental.*—The effects of coronary vein or sinus ligation are mentioned by several authors. Cohnheim found that single coronary veins could be tied without damage to the heart, but that most hearts, though not all, became cyanotic if the coronary sinus was obstructed, the left heart being most affected. In one-half hour there was great bulging of the veins, dilatation of the arteries, evidence of exudation of blood into the heart wall; the heart rate slowed and sometimes cardiac death ensued.<sup>36</sup> Several have since perfused the coronary sinus, keeping the heart alive by this means.<sup>13, 14</sup> Others have blocked the sinus or tied its veins, sometimes with marked congestion of the heart wall and exudation of blood into the myocardium and fatal results as noted by Cohnheim, sometimes with only a transient slowing or a heart block and dilatation of the coronary vessels.<sup>20, 30, 36, 37</sup> An electrocardiographic

study showed a constant increase in the height of the T-wave.<sup>37-39</sup> Cohnheim and others found that ligation of the veins accompanying an obstructed coronary artery made no difference in the result of arterial occlusion.<sup>36, 37</sup> Added to these data are the cases quoted above, where the coronary sinus was obstructed or involved in an arteriovenous aneurysm, without functional change being present in life or evidence of myocardial damage being found at autopsy.<sup>25-27</sup>

Several of the above references point to the fact that a vasodilatory substance is apparently liberated in the heart when cyanosis occurs, especially in coronary sinus obstruction followed by venous engorgement.<sup>36, 37</sup> This substance slows the heart. It is doubtless of the group spoken of as the "cardiac hormone" and belongs in the class of nucleic acid derivatives which are known to be vasodilatory, and some of which are capable of producing heart block.<sup>1-6, 9, 10</sup> Though recently the physiologic properties of adenylic acid and allied substances have been tested clinically by several for their cardioinhibitory effects with unpromising results, one report states that such preparations benefit patients suffering from intermittent elaudication, though not by vasodilatation in the affected parts apparently.<sup>7-9</sup>

The question is brought up of the wisdom of closure of the venous drainage of an area when that area's arterial supply is shut off. Recent literature indicates that the result of such a maneuver is to be based on whether or not numerous and often opposing factors will balance, so that oxidation throughout the affected portion will be enhanced.<sup>11, 40</sup> The problem is a complex physiologic one, rendering clinical decision hazardous, even precise physiologic determination of the result being impeded by the difficulties in collecting significant data. The main factors are the rate and volume of blood flow to, in, and from a part, the rate of O<sub>2</sub> utilization and the coefficient of utilization, the individual vasodilatory reaction in response to various chemical or nervous stimuli, the ability of vessels carrying blood to or from the part to change their caliber, and the fact that tissues vary within unknown limits in their anaerobic abilities from time to time and in various environments. It appears in general that, even if venous congestion following venous ligation enhances oxygen utilization and causes vasodilatation, or by other means tends to preserve a part lacking in arterial supply, at least a certain amount of tissue death, especially muscular necrosis, occurs.<sup>11, 40</sup>

#### METHOD

The experiments were acute and survival in type. In the acute experiments 6 dogs, 6 cats, 1 rabbit, and 1 monkey were used. The pressure developed in the coronary sinus when it was obstructed was measured; the pressure curve was studied, noting whether there was change in color of the heart, whether vessels dilated, or if a change in rhythm occurred. Right heart pressure was taken and general systemic effects were noted in pulse and blood pressure. Electrocardiograms were taken during

various stages to see what conduction changes took place. Pathologic studies were done in gross and by microscopic examination.

In the survival experiments 4 dogs were used. The clinical effects of coronary sinus ligation were studied and electrocardiographs were taken before and after at suitable intervals. The hearts were removed at three days, seven days, four months, and six months for gross and microscopic studies.

From another series of dogs in which coronary sinus ligation was carried out, data will be utilized occasionally, especially pathologic data from the heart of an animal sacrificed twenty-four hours after sinus ligation.

Ligation or clamping of the sinus was best done by nicking the epicardium alongside the coronary sinus and by blunt dissection freeing the sinus from its bed. During this maneuver numerous small vessels were encountered which might be ruptured unless care was taken. However, any bleeding could be controlled by pressure unless the sinus itself was torn badly. The sinus was usually tied or clamped within 1 cm. of its entrance into the right auricle. If the middle cardiac vein, in the posterior or inferior longitudinal sulcus, entered the sinus proximal to the sinus blockage, it was separately ligated to occlude completely all venous drainage from the left heart wall; and in some such hearts this final step brought about left heart congestion not previously present. Sinus pressure was studied by inserting a short-tipped cannula through the right auricular appendage and passing it across the auricle into the mouth of the sinus. Its shoulders efficiently plugged the sinus opening while the short point just entered the sinus itself. The animals' thoraces were opened through the fourth left or right costal interspace. The anesthesia was ether, delivered by a mechanically interrupted positive pressure machine. In survival experiments aseptic technique was used, the chests being closed in layers without drainage.

The electrocardiograms were taken throughout the acute experiments and, while the hearts were exposed in survival experiments, by the usual three leads and by a fourth direct lead. Additional preoperative and postoperative curves were taken in survival experiments with the animal standing, lying on its back, and lying on one side.

#### OBSERVATIONS

*Acute Experiments.*—Observations in these are conveniently grouped as noted by inspection and pressure curves, by electrocardiograms and pathologic changes.

Changes in appearance on ligation or other obstruction of the coronary sinus varied between both species and individuals. In 10 dogs used in this study, 9 showed marked bluing of the left ventricular wall with dilatation of veins and then dilatation of the coronary arteries and variations in rhythm, while only 3 out of the later series of 12 dogs showed

study showed a constant increase in the height of the T-wave.<sup>37-39</sup> Cohnheim and others found that ligation of the veins accompanying an obstructed coronary artery made no difference in the result of arterial occlusion.<sup>36, 37</sup> Added to these data are the cases quoted above, where the coronary sinus was obstructed or involved in an arteriovenous aneurysm, without functional change being present in life or evidence of myocardial damage being found at autopsy.<sup>25-27</sup>

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congestion, and vascular dilatation developed petechial-like spots along the course of the larger vessels. These spots were more common toward the base of the heart. They were also very common over areas of vascular anastomoses, such as the conus arteriosus or the apical region, where so many new vessels had appeared. As noted below, these spots, upon microscopic study, were found to be made up of tremendously dilated capillary vessels, extravasation of blood from ruptured vessels being found present only occasionally (Fig. 6).

While these vascular changes were taking place, clear fluid formed beneath the epicardium alongside the larger vessels and became maximal in amount in about two minutes. It then gradually appeared about other and smaller vessels, seeming to spread along vessels, and away from vessels, along their branches, lifting the epicardium en route (Fig. 7).

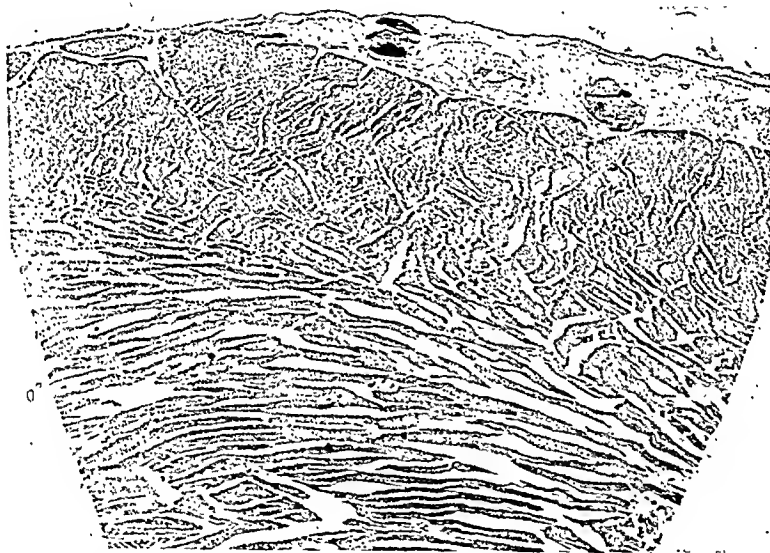


Fig. 7.—Photomicrograph illustrating acute changes in left heart wall of dog when left heart had become congested following coronary sinus closure. There is marked exudation of serous and sometimes hemorrhagic fluid about the vessels and under the epicardium.

The changes in rhythm noted set in with the vascular responses. The heart slowed rapidly and at the same time lost contractility and dilated, the effect being vagal-like. Extrasystoles were common. In no animal did fibrillation occur nor did death occur from cardiac failure.

It was interesting to note in several animals that after a ten- to thirty-minute period of cyanosis and congestion these and other signs of coronary sinus blockage disappeared, the fluid about the large vessels diminished, and the normal rate and contractility of the heart returned. Correspondingly the coronary sinus pressure which was being recorded and which was very high began to fall and eventually,

such changes or any change whatever. Five out of 6 cats showed moderate bluing and vasenlar dilatation when the sinus was tied. One cat, 1 rabbit, and 1 monkey showed no bluing of the heart or any other change in response to sinus ligation, or even wholesale venous ligation. Most of the hearts which turned blue over the left ventricle showed increasing vasenlar congestion and dilatation of veins, with cyanosis of the left heart during the first minute, by which time these effects had reached a maximum. The sinus was then markedly distended; the color of the left ventricle was purple; the right heart approximating the septum was blue; the auricles were unchanged. Bulging veins were especially

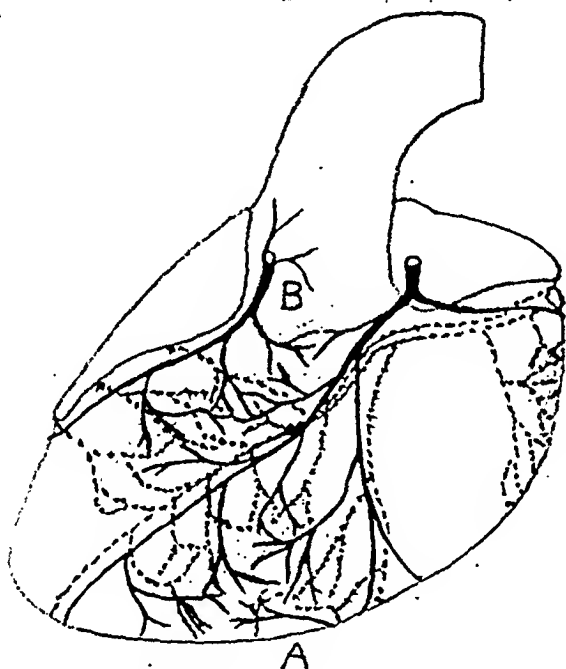


Fig. 6.—Diagram illustrating the network of small anastomosing arteries and veins which develop over the conus arteriosus (B) and about the apex of the heart (A) after coronary sinus ligation has produced congestion of the left heart wall.

marked about the apex where the posterior veins of the left ventricle, branches of the great cardiac vein, and branches of some of the right heart veins anastomose. Venous dilatation over the conus arteriosus also was marked. In these areas especially the arteries were much dilated and many fine vessels appeared in and beneath the epicardium. These could not always be identified as arteriolar, but many were much smaller than those arteries ordinarily seen over the heart's surface. They were seen also over the ascending aorta and the pulmonary artery where the main vasa vasorum stood out prominently. The main coronary arteries were much dilated. Hearts showing marked cyanosis,

graph, coronary sinus pressure in dog hearts, which had become cyanotic on coronary sinus closure, rose slowly to a point approximating that exerted in the heart wall (about 120 mm. Hg). This pressure was undoubtedly dependent on the pressure developed during systole by tension on the intramural veins and on the blood in veins between the heart walls and the epicardium. In diastole pressure fell off toward zero but where marked cyanosis was present pressure rarely fell below 40 mm. Hg before the next systolic rise (Fig. 8). Where there was no congestive response to sinus obstruction, the pressure rose but to a less extent, a high point of 60 to 80 mm. Hg being reached. Carotid or

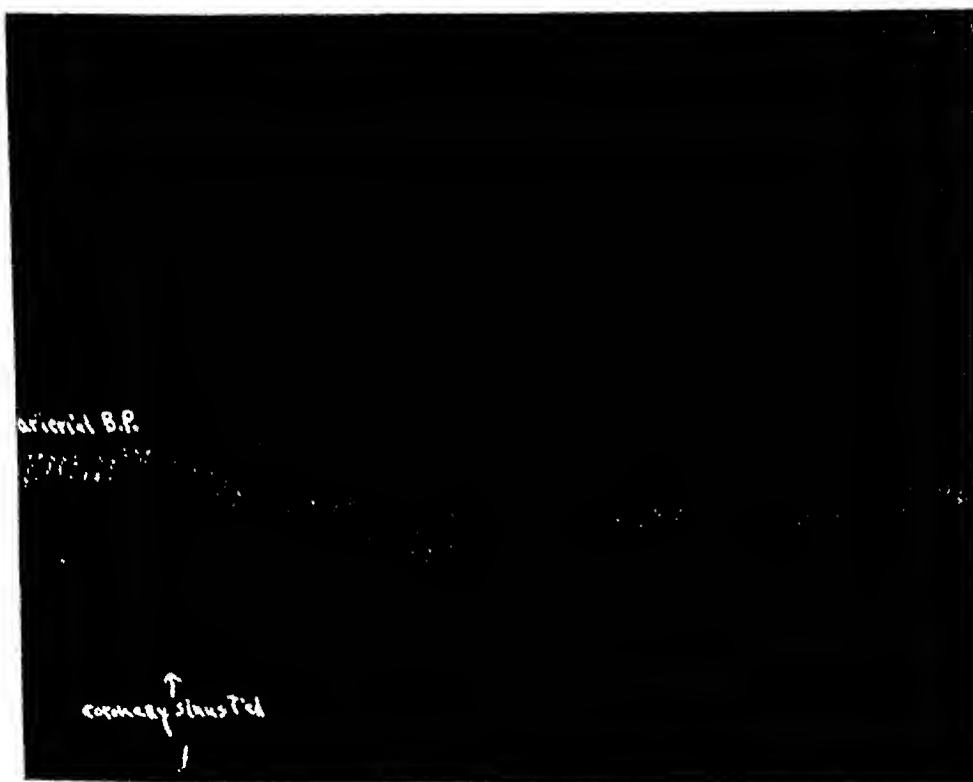


Fig. 9.—Tracing illustrating typical fall in carotid blood pressure curve after ligation of the coronary sinus in a dog whose left heart became cyanosed and congested; and then gradual recovery in blood pressure.

femoral pressure curves, when the heart was congested, occasionally showed a slight fall of from 10 to 20 mm. Hg, which tended to rise slowly if the sinus obstruction was continued and rose promptly if sinus flow was resumed (Figs. 8 and 9). Right heart and pulmonary artery pressure did not change. Cats and the one rabbit used gave similar pressure curves.

In all animals, when the sinus obstruction was removed with a return of normal appearance and function, there was a return to normal of the various pressure curves (Fig. 8).

when the heart appeared normal, approximated the level of curve shown by animals whose hearts were not affected at all by blockage of the sinus.

Unclamping or unblocking the sinus in a heart showing the usual responses led to immediate restoration of normal appearance and action except where cyanosis and congestion had been prolonged. Then, although normal function was resumed, small petechial spots or bruised areas might remain with more or less elevation of the perivascular epicardium by the clear fluid which, as noted above, had accumulated about the vessels during the sinus occlusion.

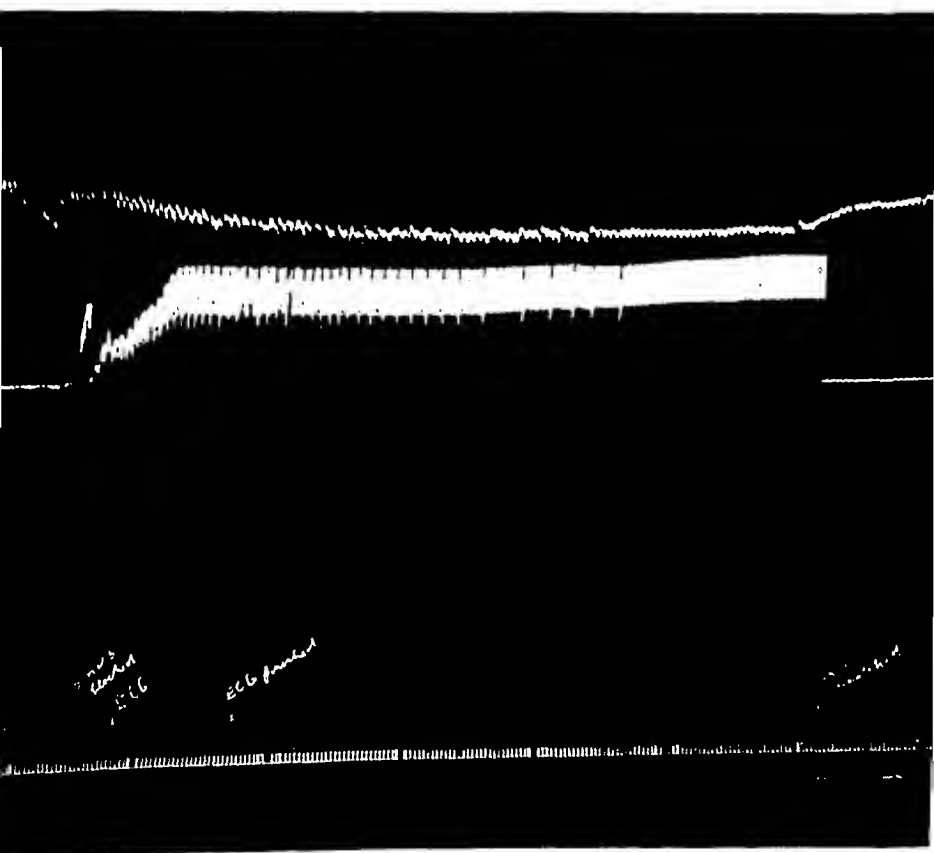


Fig. 8.—Tracing to illustrate typical carotid artery and coronary sinus pressure changes during occlusion of the coronary sinus of a dog's heart, the left heart of which became cyanotic and congested. A, Carotid pressure; B, coronary sinus pressure.

Section of the nerves to the heart was found to have no effect on the phenomenon. Though the vasodilatation seen might have been merely the result of cardiac anoxemia and increased coronary venous pressure, the marked slowing of the heart was against such an assumption.

The pressure curves corresponded excellently with the naked-eye appearances of increased venous pressure. As in the accompanying

*Survival Experiments.*—Observations are here noted under clinical, pathologic, and electrocardiographic changes. Data were obtained from four dogs of this study and pathologic data were used from another study for a description of the changes found twenty-four hours after coronary sinus closure. The four of this series showed the typical reaction with bluing of the left heart and vascular dilatation, as noted above. Two were markedly affected, it being feared that the animals would not survive. However, in these, when the pericardium was closed, contraction became stronger and several hours afterward, when the animal had recovered from ether, the pulse was strong and regular. The animals could stand without trouble a few hours after operation. Though not playful for several days, they could climb stairs without dyspnea on the first day. The other two dogs, whose hearts had turned blue but had not dilated so much, seemed no worse for the operation. They soon played quite normally and showed no change in exercise tolerance.

The pathologic changes were noted by sacrifice of the four animals of this series at three days, seven days, four months, and six months.

Upon opening the chests of other dogs twenty-four hours after ligation of the coronary sinus had produced the typical acute changes of congestion, bradycardia, etc., a characteristic bruised appearance was seen over the left ventricle, conforming to the area of congestion and cyanosis. No dilatation of the main veins was seen though in areas of anastomoses, as over the conus arteriosus and about the apex of the heart, numerous and prominent vessels, both arterial and venous, were seen (Fig. 6). An elevation of the epicardium along the main vessels was still present, produced by an accumulation of opaque material, while spreading from the main vessels were grayish opacities just beneath the epicardium. The opaque material was apparently organized serous fluid. Petechial-like spots were still usually present but were decreased in number. Microscopic examination of sections stained by hematoxylin and eosin demonstrated changes in the bruised areas varying from early edema and cloudy swelling with granulation of muscle fibers to typical necrosis of muscle following congestion and hemorrhagic infarction described by Middleton.<sup>12</sup> The necrosis usually existed only in the outer one-sixth of the left heart and was rarely found in the right heart. Some portions of the left heart were more severely damaged, necrotic patches being present, as deeply as the midportion of the wall. Beneath the epicardium of the left ventricle and scattered throughout the outer one-half of the wall were greatly distended venous channels and smaller vessels of capillary size. Some of these had ruptured, extravasating their contents nearby and rupturing surrounding muscle tissues or tearing epicardium away from the myocardium. Sections of the inner part of the left wall showed areas of vascular dilatation and capillaries were dilated. None were ruptured nor was there perivascular exudate or transudate. The petechial-like areas were found

The electrocardiographic changes, as a rule, were irrelevant and related to manipulation usually. In several, however, a splintering of the QRS complex occurred immediately closure of the sinus was accomplished. It disappeared within a few minutes of reopening the sinus or, in hearts which balanced their venous drainage while the sinus was still closed, presumably by dilatation of the thebesian vessel, the splintering diminished and disappeared as the color of the heart improved (Fig. 10).

Gross pathologic examination of specimens added nothing further to the above changes except that on cross section marked congestion of the left ventricular wall was seen. Sometimes the right ventricular wall near the septum was also congested. In the outer one-third of the left wall extravasation of blood was frequently apparent. Microscopic studies confirmed the dilatation of vessels as noted above. Vessels, especially veins, throughout the left ventricular wall were always larger than usual if congestion had been well marked. The epicardium

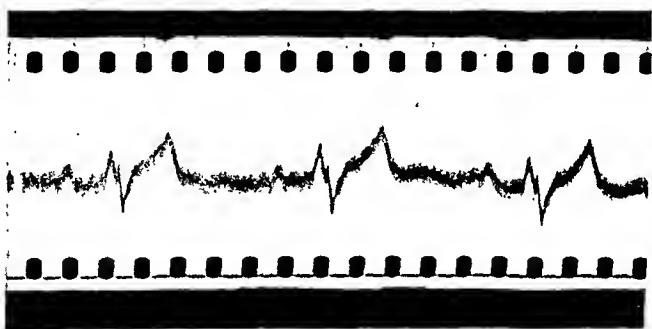


Fig. 10.—Electrocardiographic tracing to show typical splintering of QRS complex after occlusion of coronary sinus of dog's heart had produced congestion and cyanosis of the left heart.

about the larger vessels was raised, the spaces being filled with pinkish fluid as stained by hematoxylin-eosin after paraffin section. The fluid occasionally contained blood cells or tissue debris. Though no lining cells were definitely identified, it was felt that these perivascular spaces were dilated lymph channels. Their distribution certainly corresponded to that of the cardiac lymphatics as outlined by Kampmeier.<sup>41</sup> Within the heart wall these spaces were not seen. The petechial-like spots noted above on section usually showed dilated capillaries, but sometimes these had ruptured and there was extravasation of blood. This occurred chiefly just at or under the epicardium but was common in the outer one-third of the heart wall and rare in the inner one-third. Occasionally the myocardium was ruptured, especially at the epicardial surface, the epicardium then being torn from the muscle fibers by extravasation of blood or by exudation of the clear pink staining fluid in the neighborhood of the larger coronary vessels (Figs. 7 and 11).

epicardial patches diffusely distributed around the smaller superficial vessels were found to consist of collections of pink staining material more or less dotted by blood cells and remnants of muscle or connective tissue cells. There was no limiting membrane found around these collections nor were they definitely associated with the larger spaces about the main coronary vessels (Figs. 11 and 12).

The heart of a dog sacrificed on the third postoperative day showed similar bruising of the left heart. There was no evident dilatation of the large arteries or veins. In the anastomotic areas about the apex and across the conus arteriosus, enlarged medium and small vessels were conspicuous (Fig. 6). The main vessels were still more or less surrounded by a grayish subepicardial material and scattered patches of an apparently similar nature lay along or around smaller vessels. No petechiae were seen. Microscopic examination revealed necrosis in the outer one-sixth of the left ventricular wall much more marked than in the twenty-four-hour specimens. Some portions of the left heart were more severely damaged than others, necrosis extending to the midpart of the wall with rupture of vessels and extravasation of blood both superficially and deeply. In the inner half of the left ventricle, in areas corresponding to these outer necrotic parts, marked dilatation of veins was present, while arterioles and capillary vessels were also dilated. The right ventricle showed only occasional and small areas of connective tissue reaction, chiefly in the outer one-sixth, with myocardial fibrillation and vacuolization. Where the epicardium had been raised from the myocardium or away from the larger vessels, with extravasation of blood or the occupation of these areas by the homogeneous material described above, connective tissue proliferation was now seen with well-advanced organization. Such connective tissue organization was also well started in those areas deeper in the wall where extravasation of blood with rupture of muscle had taken place as well as about areas of necrosis (Fig. 12).

The heart of a dog sacrificed after seven days showed no bruising of the left heart. Only a slightly prominent collection of grayish material was present about the larger left coronary vessels. No bulging of the sinus or the larger veins or the arteries was seen. There was definite enlargement of the veins about the apex of the heart which carried on an anastomosis between the veins of the left heart and the posterior veins of the right heart emptying into the right auricle. The veins of the left ventricle also anastomosed with the right heart veins by enlarged vessels over the conus arteriosus. Many new and prominent vessels of venular or arteriolar size were present in these parts. Various sections from the left ventricle demonstrated very slight swelling of muscle cells with occasional nuclear changes and separation of cells in the outer one-third of the wall. There were very rare patches of necrosis or other evidence of hemorrhagic infarction. There was very little of

mostly to be widely dilated capillaries but sometimes extravasation of blood was also present in these areas. The grayish elevated markings alongside the larger superficial blood vessels were found to contain

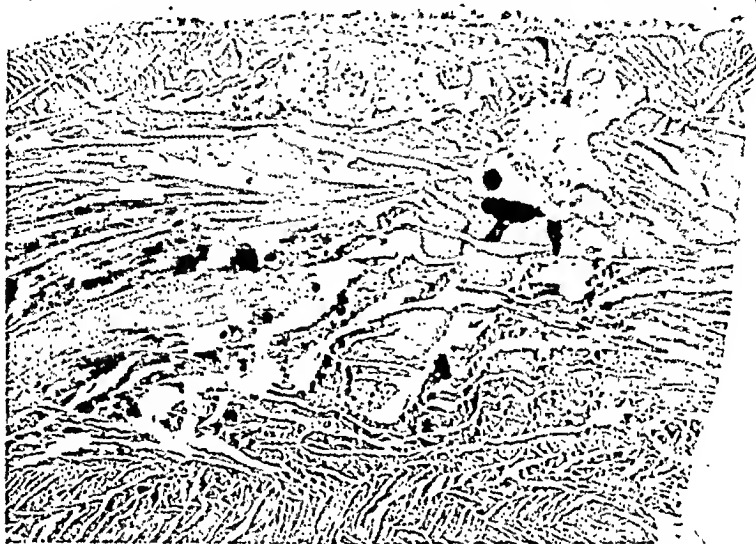


Fig. 11.—Photomicrograph of section of left heart wall twenty-four hours after ligation of coronary sinus had produced congestion of left heart in dog. Some areas of necrosis are seen in center of section.



Fig. 12.—Photomicrograph to illustrate necrosis in dog's left heart wall after coronary sinus obstruction had caused cyanosis and congestion of left heart.

pink staining homogeneous material in which white cells and connective tissue cells were scattered. No definite endothelial or mesothelial wall could be made out for these spaces as a rule. The grayish sub-

epicardial patches diffusely distributed around the smaller superficial vessels were found to consist of collections of pink staining material more or less dotted by blood cells and remnants of muscle or connective tissue cells. There was no limiting membrane found around these collections nor were they definitely associated with the larger spaces about the main coronary vessels (Figs. 11 and 12).

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the pink staining perivascular material noted above. What was found was well organized. The right heart muscle was intact.

A heart examined four months after the sinus was tied presented no enlargement of the main vessels. There were gray streakings and patches alongside the large vessels of the right heart. A whorl of veins and arteries not normally present was found at the apex, and the veins and arteries across the *commissura arteriosus* were unusually large and numerous. Sections from the left heart showed subepicardial scarring about the larger vessels, corresponding to the gray streakings seen in the gross. Around larger vessels in the outer one-half of the wall scarring of myocardium was seen. The right heart was normal on section.

Six months after sinus ligation a heart presented no enlarged vessels even at the apex or over the *commissura arteriosus*. Subepicardial scarring was present around the larger vessels and scarred areas were seen associated with larger vessels in the outer one-half of the wall.

Both the four-month and the six-month postoperative specimens had an increased number of vessels of a venous nature in the inner part of the left ventricular wall (Fig. 4).

The characteristic change in the electrocardiograms was a splintering of the QRS complex (Fig. 10). This change paralleled the onset of left heart cyanosis, dilatation of the coronary vessels, and the bradycardia. This splintering in acute experiments always disappeared if the sinus were unclamped and it always disappeared in survival experiments after several days when, as noted above, dilatation of the coronary sinus and the phase of acute left heart congestion was ended. Extrasystoles and flutter were noted, but only while the heart was exposed. The T-wave was so variable that no statement could be made regarding its changes.

#### DISCUSSION

It appears that ligation of one or several of the coronary veins of the human heart is unlikely to produce significant trauma to the heart or interference with function. Ligation of the coronary sinus in animals is occasionally followed by a marked vasodilatation of the coronary vessels, slowing of the heart, and later hemorrhagic infarction and muscular necrosis of the left ventricular wall. This reaction might occur in human hearts and would be dangerous, though perhaps not fatal. Just as in animal studies, human hearts would doubtless differ in their reaction to venous obstruction, some likely showing no change whatever. Hemorrhage from cardiac veins can therefore be checked fairly safely either by pressure and ligation or by ligation alone.

Whether or not ligation of the cardiac veins in man would result in pain cannot be definitely stated. Presuming that, as regards pain, the effects of coronary vein or sinus occlusion could be compared to the

effects of coronary artery ligation, it is unlikely that pain would be produced. Several cases are reported in which large coronary arteries, and usually the veins also, were tied off during suture of a stab wound of the heart, and in which no pain resembling that of coronary thrombosis or angina pectoris was evident at any time. No general anesthetic was used in these cases, mere local infiltration of the precordium being done. That some infarction had occurred was proved by electrocardiography.<sup>42, 43</sup> Cases suffering from coronary thrombosis, with comparable areas of myocardial infarction following on similar amounts of coronary artery occlusion, present a wide variation in the pain response. Pain in the experimental animal is hard to assess. Severe pain evidently results from acute coronary artery occlusion in the conscious animal.<sup>44-47</sup> However, dogs that have had large coronary arteries ligated under ether anesthesia sometimes appear perfectly free of pain immediately on recovery from anesthesia, while others, though perhaps uncomfortable, suffer no acute pain. The same variation in reaction is seen in dogs that have had the coronary sinus closed and have exhibited similar amounts of left heart cyanosis and congestion, some appearing absolutely free from pain, others appearing somewhat miserable but not being actually in pain. Finally, if it were true that the pain of occlusive lesions of the coronary arteries depended solely on relative oxygen deficiency in functioning myocardium and that the same held true for occlusion of the coronary veins and the coronary sinus, it would be unusual for pain to be produced by the later lesion. Hearts of different species vary widely in the amount of congestion, cyanosis, and infarction that follows on ligation of even the coronary sinus; many show no change whatever, and, as pointed out above, even those that do exhibit congestion and cyanosis after sinus occlusion give no evidence of pain.

The vasodilatory reaction seen in some animals following coronary sinus occlusion resembles the reaction following the application to the heart of vasodilators, such as adenosine or adenylic acid.<sup>1-6</sup> The reaction following coronary sinus ligation occurred after all the nerves to the heart had been severed. It is possible, of course, that the vasodilatation was due merely to a combination of cardiac anoxemia and increased pressure in the coronary vascular system, but the slowing of the heart beat was against such an explanation. In such reactions not only do the coronary vessels dilate, but the heart is slowed and perhaps the likelihood of fibrillation is lessened.<sup>1-4</sup> It would be obviously impractical and dangerous to tie the coronary sinus to produce such a reaction when the nutrition of the heart became deficient through coronary artery occlusion. It would seem expedient, however, to test the effects of vasodilatory substances, such as adenylic acid or adenosine, when applied directly to ischemic heart muscle. Intravenous use of adenylic acid and related substances appears to be relatively ineffective in animals and in man, possibly because of its rapid loss of potency once free in the blood stream.<sup>2, 3, 5</sup> As adenylic acid rapidly loses its potency when free

in the body, it would need to be applied constantly to the heart, but in such quantity that coronary artery vasodilatation would be maintained, without a general vasodilatation occurring, with a fall in blood pressure and a consequent slowing effect on the coronary inflow. Such a procedure might minimize the effects of coronary occlusion. In several animal experiments this result has been demonstrated. It must be remembered, however, that, when coronary thrombosis occurs, accessory vessels may be too sclerosed to dilate adequately. Moreover, nearly all cases of coronary thrombosis show a marked fall in blood pressure and in some cases aortic blood pressure might be so reduced that coronary vasodilatation might slow coronary blood flow enough to further thrombosis. There is also the question of whether adenosine might behave like some nucleic acid derivatives and produce an increased local leucocytosis detrimental to both the heart and pericardium. In a recent report insulin-free pancreatic extract, a skeletal muscle extract, adenosine phosphoric acid, and adenosine, administered intramuscularly, have been found to inhibit intermittent claudication to a degree. The drugs thus administered were quite harmless. The beneficial effect was thought to be due not to vasodilatation, but to the addition of some substance to ischemic contracting muscle without which pain occurred.<sup>9</sup>

The pathologic data noted above confirm the opinion that closure of an area's venous outflow, when its arterial inflow is shut off, is not without danger.<sup>11, 40</sup> In the heart when venous outflow interruption did produce a vasodilatory reaction, more or less muscular necrosis ensued for the reaction appears to be brought about only when venous congestion occurs. This result occurred not only if the venous outflow alone was tied, but when one of the main coronary vessels also was tied. It is true that the results of such experiments on the heart cannot be too closely applied to the results of similar procedures on a limb. The heart at each contraction elevates the cardiac intravenous pressure markedly. This may force blood out of the heart wall via the thebesian vessels and avoid too extreme and dangerous engorgement. This may be done so efficiently that no venous blood is actually retained and no congestion of the heart wall and subsequent vasodilatation results. On the other hand, such pressure elevations are sometimes sufficient to rupture vessels and cause local areas of myocardial necrosis. Besides this functional difference between the heart and other parts, the coronary circulation is prone to overlap and thus provide numerous anastomoses in such a way that ligation of one coronary artery does not leave a preparation very closely resembling a limb with its main artery tied. It seems reasonable to suppose that when, by tying the venous outflow of a limb, the chances of gangrene are diminished, this result is accomplished because venous blood cannot find easy exitus, congestion ensues and vasodilatation, with also more or less tissue death, especially muscular necrosis.

The evident function of the thebesian system of vessels, which functionally includes the network of small vessels connected with arteries and

described by Vieussens, is to carry blood into the heart cavities or into the epicardial venous network during cardiac contraction and thus to empty the heart wall. It would seem improbable that in either normal or abnormal hearts this function should be reversed so that in ventricular systole blood would flow into the heart wall along the thebesian vessels, or the vessels of Vieussens, against a high intramural pressure and against the outflow of venous blood. In hearts exhibiting coronary artery occlusion during diastole and early auricular systole, such a possibility might be entertained in spite of low intraventricular pressure, because the coronary artery inflow, which ordinarily occurs during this period and tends to bulge the heart wall and close the slitlike endocardial openings of the thebesian network, would be diminished. The most favorable time would appear to be early in auricular systole as intraventricular pressure is rising and coronary inflow is falling off, but at the same time intramural pressure is also rising and venous blood is about to be forced from the heart wall (Fig. 5). It was found that by coronary sinus ligation it was possible to enlarge the thebesian-like vessels of the heart wall (Fig. 4). Recently a series of hearts so prepared was subjected to coronary artery ligations. They did not appear to gain adequate nutrition via the dilated thebesian-like vessels, for, when vascular adhesions that had formed during the experiments between the heart wall and various structures of the thoracic cavity were separated, the hearts failed through lack of blood supply.<sup>48</sup>

It seems that, as Stella contended after experiments on perfused hearts, a thebesian vessel backflow into the heart wall is improbable. In criticism of Stella's work it has been said that his experiments were a too brief test of the backflow theory and that longer experiments were in order.<sup>18, 19, 32</sup> It appears, however, that even in the intact healthy animal and even after the thebesian network of the heart has been dilated over a long period, no backflow takes place when the coronary arteries are gradually closed.<sup>45</sup>

A flow of blood from the right auricle into the coronary sinus and thus to the heart wall seems improbable and in any event unlikely adequately to nourish the heart. Such a flow seems possible during two very short periods. Very early in auricular systole blood might be forced into the coronary sinus if the sinus outflow had not already become augmented too greatly. Early in diastole a coronary sinus backflow might occur as the intra-auricular pressure rises, intramural pressure falls, and sinus outflow is decreased. Later in diastole very little pressure exists within the right auricle and, unless coronary occlusion were marked, coronary inflow, by filling the heart wall, would leave little space for any venous backflow into the myocardium (Fig. 5). No evidence of a suction of blood along the sinns into the heart wall was seen in these experiments.

Congestion and cyanosis of the left ventricular wall, following occlusion of the coronary sinns, give a constant splintering of the QRS com-

plex, W or M in fashion (Fig. 10). Similar electrocardiographic findings have been reported in studies on man. The phenomenon is rarely found in the normal, but it is apparently closely associated with occlusive lesions of the coronary arteries or with myocardial disease.<sup>49-51</sup> It would seem that lack of normal blood supply and congestion of the heart muscle from other causes than occlusion of the coronary arteries might give electrocardiographic findings similar to those of coronary artery occlusion. It might be that in experimental studies of coronary artery closure care should be taken not to include the vein with the artery, though thus far several report that this circumstance has given rise to no change from the usual picture of coronary artery closure.<sup>37-39</sup> In autopsies on patients dying of coronary disease examination of the venous system of the heart should not be neglected, especially where splintering of the QRS complex has been present. The splintering of the QRS complex commenced with left heart congestion, vasodilatation, and cardiac slowing and remained present in acute experiments until the sinus was unblocked and congestion disappeared. In the survival experiments, where marked congestion of the left heart occurred with splintering of the QRS complex, the splintering disappeared in about twenty-four hours or at about the time congestion would be disappearing as judged by pathologic studies. It seems that congestion, cyanosis, and anoxemia of the heart wall account for the splintering effect. The typical changes of coronary occlusion have previously been attributed by various workers to myocardial ischemia and oxygen lack alone.<sup>30, 52</sup> However, it is also during the stage of rapidly progressing cellular trauma and death that the splintering of the QRS complex is seen. After twenty-four to forty-eight hours the acute degenerative changes have mostly taken place in the heart wall and resolution with fibrosis has commenced.

#### SUMMARY

1. Variations in cardiac function and morphology, produced by coronary sinus occlusion, or by occlusion of the veins of the heart, depend on the varying number and efficiency of the venous and thebesian anastomoses which drain the heart wall. Thus, with insufficient or inefficient venous and thebesian anastomoses large enough degrees of venous occlusion may produce congestion of the heart wall, slowing of the heart, dilatation of the veins and the arteries of the heart, and myocardial necrosis.

The coronary sinus of dogs, cats, and monkeys in many instances can be completely and suddenly occluded, where it enters the right auricle, without producing any significant change in cardiac function or morphology. Sometimes, however, in dogs especially, left heart congestion occurs, with slowing of the heart, dilatation of both the arteries and the veins, and a moderate to severe degree of myocardial necrosis. Such a reaction does not usually endanger cardiac function gravely. In a large

series of dogs no death occurred from the effects of coronary sinus ligation, but the myocardial changes produced would not prove beneficial to a heart already suffering from other pathology.

Individual cardiac veins in the dog, cat, and monkey can usually be tied without change or with very slight change in cardiac morphology. Ligation of the larger veins or of groups of veins sometimes leads to a small amount of myocardial necrosis, but produces no marked change in cardiac function or morphology.

2. Thebesian vessels can be dilated by tying the coronary sinus. In most hearts they dilate so readily that, when the coronary sinus is closed, the venous blood of the left ventricle is rapidly forced into the left ventricular cavity and no congestion ensues.

3. When venous congestion of the left heart wall occurs, following coronary sinus closure, it gives rise to a vasodilatation of the coronary vessels and to slowing of the heart. This reaction resembles that seen after intravenous or intracardiac administration of adenosine or similar substances and suggests the local application of such substances to the heart in cases of coronary thrombosis.

4. This study supports the contention that tying the main vein, from a part already deprived of its main arterial supply, is likely to cause muscular necrosis, sometimes of serious enough degree to offset any possible advantages of the procedure. Such a procedure, if it causes significant vascular congestion with increased oxygen utilization and vascular dilatation, apparently may induce muscular necrosis in the affected part.

5. A consideration of the coronary sinus outflow and pressure curves, in relation to the cardiac cycle and cardiac pressure curves, prejudices one against either a thebesian vessel backflow or a coronary sinus backflow as a source of nutrition to hearts deprived of their ordinary blood supply.

6. The occlusion of coronary veins makes no change in electrocardiographic curves. Occlusion of the coronary sinus, if no congestion and cyanosis of the left heart wall ensues, makes no change in the electrocardiographic curves. If congestion and cyanosis ensue, then splintering, M or W in form, of the QRS complex is seen. It may be that lack of oxygen in ventricular muscle accounts for this phenomenon, as it disappears in acute experiments the moment congestion is relieved by unclamping the sinus; and in survival experiments it disappears in twenty-four to forty-eight hours when left heart congestion has disappeared.

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## PHYSIOLOGIC ADJUSTMENT IN SUBLETHAL REDUCTION OF LUNG CAPACITY IN DOGS\*

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IN KEEPING pace with the recent advances in the development of chest surgery, further vital considerations arise regarding the coincidental lung changes and the compensatory respiratory physiology in intrathoracic operations. The absolute lung capacity requirement for normal respiratory function is doubtless individually variable. It may be governed by the volume of functioning lung and by the efficiency of lung tissue available. That a wide margin of safety in normal lung capacity exists in both man and animals is no longer questionable. From studies in metabolism it is well recognized that body surface area is a definite entity in determining the respiratory requirement in the human organism. In the dog a different relationship exists because of the lack of sweat glands in the skin. In this animal it is necessary for the lungs to assume the added functions of heat regulation and maintenance of water balance. Therefore, an absolute minimal functionate lung in the dog would, from a physiologic consideration, be relatively something in excess of sublethal in the human organism. Because of its acceptable size and economic accessibility the dog has been most frequently used in experimental studies of respiratory function in collapse therapy and other problems in thoracic surgery.

Thoracoplasty as such has been utilized very little in dogs. Curiously enough the mortality rate in dogs following thoracoplasty has been discouraging. However, lobectomy and pneumonectomy are now not fraught with grave danger. Collapse of a lobe or of several lobes of the lung by any method other than thoracoplasty has been very successfully performed in many laboratories. Gluck, in 1881, removed the entire lung on one side from six dogs and eight rabbits.<sup>1</sup> Two of the rabbits lived. His failure was due mainly to technical errors. Friedrich, in 1908, applying the technical principle of ligating the pulmonary vessels separately, succeeded in performing pneumonectomies without a discouraging fatality.<sup>2</sup> More recently, improvements in surgical technique have made it possible to perform the operation without mishap in from 80 to 90 per cent of the attempts.

Amputation of a lobe of the lung for tumor and for bronchiectasis in man was done as early as 1907 by Gluck,<sup>3</sup> and later was greatly improved by Sauerbruch.<sup>4</sup> Total pneumonectomy was performed in dogs

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by Rolandus in 1492.<sup>5</sup> This operation has been performed successfully on the human organism only within the last decade.<sup>6</sup> Experimental studies on diminished lung volume were begun in this clinic almost with the opening of the research laboratories in 1927. Progress in this work was enhanced by the development of a safe and reliable method of closing large bronchi.<sup>7</sup> Occlusion of the bronchus and eventual massive collapse in any lobe of the lung was accomplished by simply painting the entire circumference of the lumen of the bronchus with a 35 per cent aqueous solution of silver nitrate.<sup>8</sup> This development, coupled with improvements in surgical technique of lobectomy and pneumonectomy, paved the way for further studies on lung function. Drastich, Adams, Hastings, and Compere in 1934, found that dogs with only 50 per

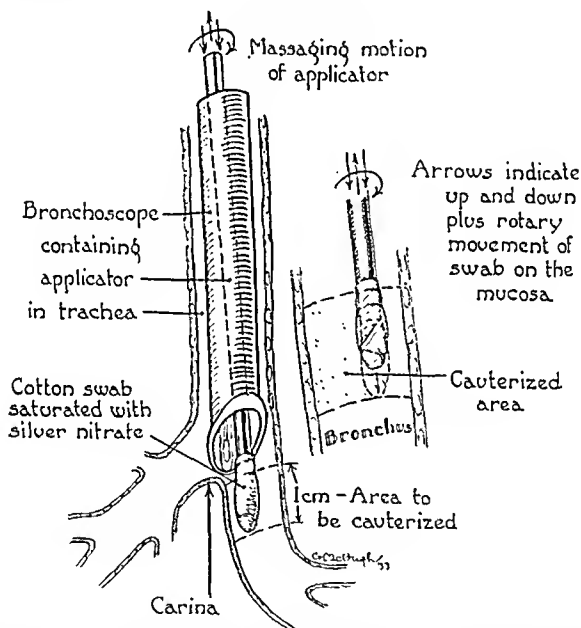


Fig. 1.—Diagrammatic illustration of the applicator containing a 35 per cent solution of silver nitrate which is being applied to the bronchial mucosa. The entire circumference of the bronchus must be cauterized, and the arrows indicate the two directions of movement during the application of the cauterizing agent.

cent of their pulmonary tissue functioning have no apparent difficulty in delivering an adequate supply of oxygen to the tissues.<sup>9</sup> They also observed that partial lung collapse leads to greater acid-base changes on exercise than does partial pneumonectomy. This variation was attributed to the fact that during rigorous exercise a significant fraction of the blood continues to flow through the remaining collapsed lung tissue. Andrus, as early as 1923, demonstrated that there was as much as 40 per cent increase in blood flow through the opposite lung within a few hours after pneumonectomy.<sup>10</sup> In later studies he observed that the respiratory volume, the pulse rate, the circulation through the aerated



Fig. 2A.—Dog 617. *a*, X-ray of chest of dog following complete atelectasis of the right lung by bronchial stenosis. Note marked shift of the mediastinal contents to the right and elevation of right diaphragm. *b*, X-ray of same dog following complete atelectasis of left lower lung lobe by bronchial stenosis. Note the spontaneous pneumothorax (right), with a shift of mediastinal contents back to the midline.

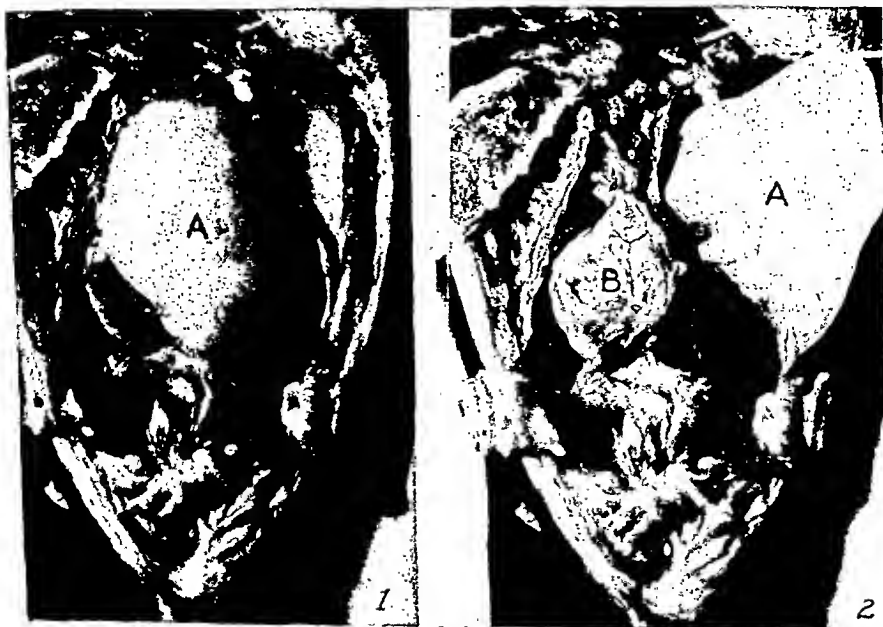


Fig. 2B.—Dog 617. 1, Photograph at autopsy twelve days following atelectasis of left lower lung lobe. Note (A) overdistended left upper lung lobe, (B) heart, (C) atelectatic right lung all shifted toward the right side. 2, Dog 617 with left upper lung lobe lifted. The atelectatic left lower lobe D is now visible. The pneumothorax had been partially reabsorbed. No fluid was present in pleural cavity.

lung, the hemoglobin, and red blood cell count were all apparently increased within twenty-four hours after ligation of the left main bronchus.<sup>11</sup> Heuer and Andrus observed a temporary rise in alveolar carbon dioxide and a fall in alveolar oxygen following pneumonectomy.<sup>12</sup> Associated with these alveolar air changes was a temporary rise in carbon dioxide content and capacity of the blood and a marked fall in oxygen content. There was also a marked decrease in the percentage



Fig. 3A.—Dog 749. Photograph of chest at autopsy two days following complete atelectasis of right lower and right middle lung lobes. The heart has been removed. Note (A) overdistended right upper lung lobe, and (B) completely atelectatic right lower, middle, and accessory lung lobes. The left lung had been extirpated. (See Table II.)

of oxygen saturation. The increase in hemoglobin persisted. After approximately one month all of these changes except the increased hemoglobin and oxygen-carrying capacity returned to normal. Adams and co-workers, in studies on vascular changes in pulmonary atelectasis, demonstrated a decreased volume flow of blood with a coincidental passive congestion of the atelectatic lung.<sup>13</sup>

Various methods have been used in attempts to produce changes characteristic of hypertrophic osteoarthropathy.<sup>14</sup> None of these procedures

has been successful. No physiologic explanation for their failure could be formulated. The present experimental studies are being carried out over a long period of time purposely in an effort to observe the eventual anatomic and physiologic status of animals with diminished lung tissue.

Investigators cited in earlier paragraphs have described the immediate changes that transpire during diminution of lung volume. We have attempted to assimilate in dogs physiologic conditions existing in the human organism after collapse therapy and after amputation of various integral units of the lungs. The technical procedure of producing diminished lung volume was carried out in stages. From one month to six weeks was usually allowed to elapse between operations on the lobes

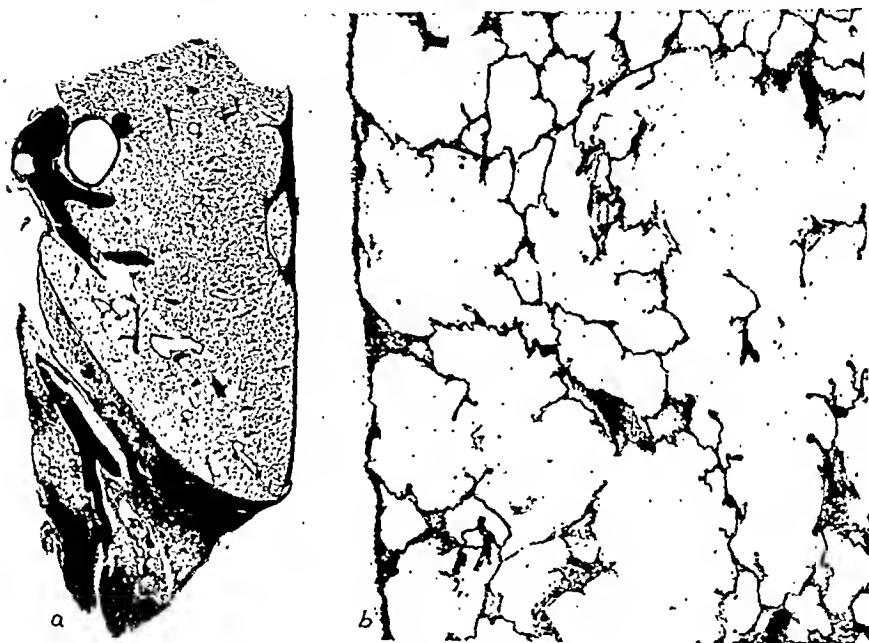


Fig. 3B.—Dog 749. *a*, Low-power microscopic section of lower half of overdistended right upper lung lobe and atelectatic right middle lung lobe. *b*, High-power photomicrograph of peripheral portion of right upper lung lobe. Note marked compensatory emphysema.

or stenoses of the bronchi. Laboratory observations were made on the dogs previous to any attempt at diminution of lung volume. Since dogs apparently withstand pneumonectomy well, the first procedure was to remove surgically the entire left lung, utilizing Friedrich's principle of separate ligation of the pulmonary vessels. Blood analyses and bronchoscopic and x-ray examinations were made at indicated intervals. The lung volume was then further decreased by stenosing individual bronchial orifices of the remaining lung. This was accomplished by the technique mentioned above. The dogs were observed at daily intervals for evidence of air hunger. There were three animals alive and active nineteen months after the institution of the experiment. These dogs

are being kept under ordinary conditions in the animal house. Occasional observations are made on their blood to note the effect of this prolonged diminished lung capacity. These observations will be reported at a future date.



Fig. 4A.—Dog 748. X-ray of chest following iodized oil filling of bronchial tree (Feb. 8, 1938). (See Table I for date of collapse of various lung lobes.) Only the right upper and middle lobe bronchi are open. Note pneumothorax on left.

#### PROTOCOL OF DOG 748

The lung capacity was reduced subtotally by bronchial stenosis and atelectasis of over two years' duration. The right upper lobe remains inflated; the dog is well and active.

Sept. 21, 1937: The dog was a healthy appearing male mongrel weighing 9.0 kg. Bronchoscopy was carried out under morphine anesthesia. The left upper and lower lobe bronchi were cauterized with a 35 per cent solution of silver nitrate.

Oct. 5, 1937. Bronchoscopy: The left primary bronchus was almost completely stenosed; it was recatherized with  $\text{AgNO}_3$ . The right lower lobe bronchus was cauterized with a 35 per cent solution of silver nitrate.

Oct. 8, 1937. Bronchoscopy: The left primary bronchus was occluded. The right lower lobe bronchus presented a 3 mm. opening.  $\text{AgNO}_3$  was applied to the right lower and accessory (subcardiac) lobe bronchi.

Jan. 15, 1938. Bronchoscopy: The right lower and accessory lobe bronchi were occluded. X-ray examination of the chest showed the heart and atelectatic left lung in the left half of the lung field. No pneumothorax was present.

Feb. 8, 1938: Intrapleural pressure readings were:

	EXPIRATION	INSPIRATION
Left	11 cm. H <sub>2</sub> O	14 cm. H <sub>2</sub> O
Right	9 cm. H <sub>2</sub> O	11 cm. H <sub>2</sub> O

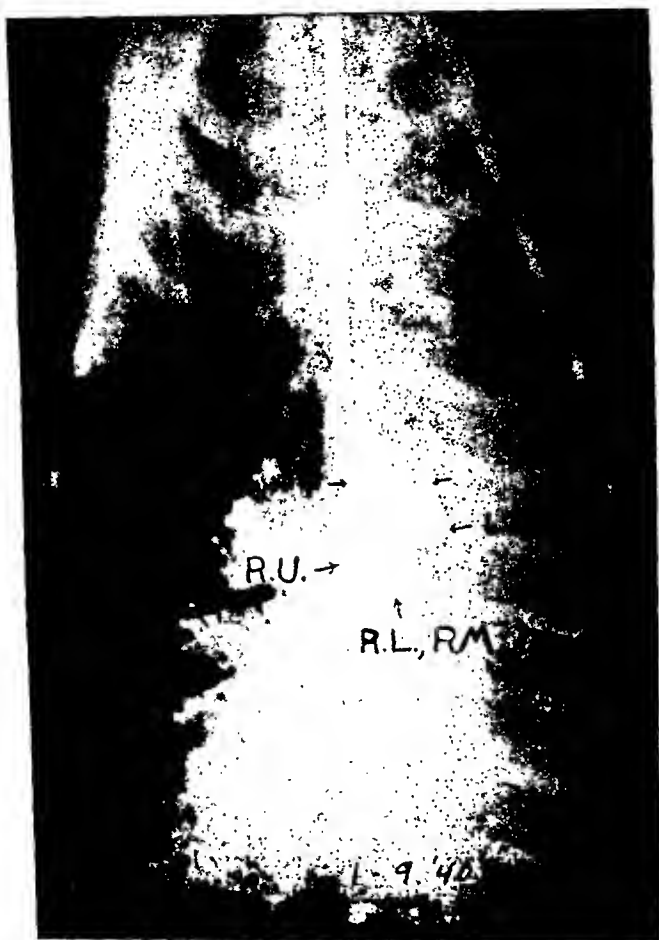


Fig. 4B.—X-ray of chest of Dog 748 on Jan. 9, 1940, following iodized oil filling of the bronchial tree. Only the right upper lobe bronchus is open, all others having been closed by silver nitrate cauterization. No pneumothorax remains at this time.

Bronchography (Fig. 4A): All bronchi except the right upper and middle were occluded. A pneumothorax on the left side was produced by needle puncture of the right lung.

April 19, 1938. Fluoroscopy and x-ray: The pneumothorax on the left side was completely reabsorbed. The dog was active and healthy. Bronchoscopy showed no change since January 15.

Dec. 6, 1938. Blood analysis: Hemoglobin, 90 per cent; hematocrit, 60 per cent; red blood count, 5,000,000; CO<sub>2</sub>, 30.6 per cent; O<sub>2</sub>, 17.4 per cent.

Dec. 17, 1938. Bronchoscopy: The right middle lobe bronchus was cauterized with a 35 per cent solution of silver nitrate.

Jan. 21, 1939. The dog was active and apparently normal when at rest. Exercise produced dyspnea. Bronchoscopy showed that the right middle lobe bronchus was occluded.

Jan. 23, 1939. Blood analysis: Hemoglobin, 105.0 per cent; hematocrit, 55.0 per cent; red blood count, 6,400,000;  $\text{CO}_2$ , 29.2 per cent;  $\text{O}_2$ , 26.0 per cent.

Jan. 26, 1939: X-ray examination showed no pneumothorax.

April 29, 1939. Fluoroscopy: There was no change since January 26. The dog was active and healthy and became dyspneic only on exertion.

Aug. 12, 1939. Bronchoscopy: Only the right upper lobe bronchus remained unoccluded. This bronchial lumen had increased in size.

Jan. 9, 1940. Bronchography (Fig. 4B): The dog was healthy and active over two years following the first collapse of lung tissue.

#### PROTOCOL OF DOG 24

The lung capacity was reduced subtotally by resection of lung lobes and by bronchial stenosis. The right upper lobe remained inflated.

Oct. 10, 1938: The dog was a healthy appearing male mongrel weighing 12.0 kg. Results of a blood analysis were: Hemoglobin, 95.0 per cent; hematocrit, 57.0 per cent; red blood count, 5,900,000;  $\text{CO}_2$ , 27.3 per cent;  $\text{O}_2$ , 13.3 per cent.

Oct. 15, 1938. Blood analysis: Hemoglobin, 97.0 per cent; hematocrit, 55.0 per cent; red blood count, 6,000,000;  $\text{CO}_2$ , 23.7 per cent;  $\text{O}_2$ , 25.1 per cent.

Nov. 17, 1938: The left lung was resected.

Dec. 8, 1938. Blood analysis: Hemoglobin, 104 per cent; hematocrit, 64 per cent; red blood count, 8,500,000;  $\text{CO}_2$ , 27.9 per cent;  $\text{O}_2$ , 19.1 per cent.

Bronchoscopy: The right lower lobe bronchus was cauterized with a 35 per cent solution of silver nitrate.

Dec. 13, 1938: X-ray of the chest revealed a small pneumothorax persisting in the left costophrenic angle.

Dec. 29, 1938. Blood analysis: Hemoglobin, 115 per cent; hematocrit, 54.0 per cent; red blood count, 6,000,000;  $\text{CO}_2$ , 29.4 per cent;  $\text{O}_2$ , 20.8 per cent.

Jan. 27, 1939. Bronchoscopy: The right lower lobe bronchus was completely occluded (probably since Dec. 30, 1938). Cautey was applied to the right middle lobe bronchus.

Feb. 23, 1939. Blood analysis: Hemoglobin, 90.0 per cent; hematocrit, 48.0 per cent; red blood count, 7,500,000;  $\text{CO}_2$ , 34.9 per cent;  $\text{O}_2$ , 23.7 per cent.

Feb. 25, 1939. Bronchoscopy: The right accessory lobe bronchus was occluded. Only the right upper lobe bronchus remained open and it had increased in size.

July 29, 1939: Bronchoscopy showed no change since March 18.

Oct. 11, 1939: X-ray of the chest revealed a cardiac shadow adjacent to the left chest wall. No pneumothorax was visible.

Jan. 16, 1940: The dog is active and healthy and becomes dyspneic only on exertion.

#### DISCUSSION

The dog's ability to tolerate marked reduction of lung capacity appears to be governed largely by the rate at which the diminution is carried out. When the procedure was hastened the animals either died from acute air hunger or from spontaneous pneumothorax. This became particularly obvious after the initial reduction of 43 per cent had been accomplished by left pneumonectomy. Further reduction needed

to be made with caution. Experience has shown a four- to six-week interval to be about the minimum time necessary before further reduction of lung capacity can be tolerated. Further, a reduction at this time of as much as 50 per cent of the remaining lung function was found to be an unsafe procedure (see Dog 617, Table I, and Dog 749, Table II). This principle may be applied clinically in the treatment of bronchiectasis where bilateral operations are necessary to eradicate the disease process. It also demonstrates that high positive pressure anesthesia with face mask or intratracheal catheter is unnecessary in intrathoracic operations since a high reserve of respiratory function is available.<sup>15</sup>

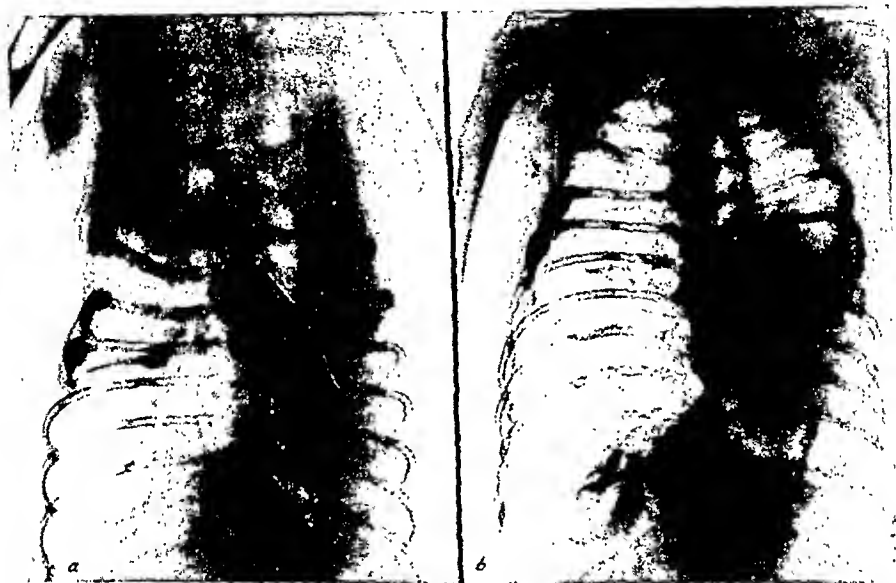


Fig. 5.—Dog 795. *a*, X-ray of chest following left pneumonectomy and right lower and accessory bilobectomy (see Table II). Note opacity in upper half of lung fields. Bronchoscopic examination revealed frank pus exuding from the right upper lung lobe bronchus. The right middle lobe bronchus was clear. *b*, X-ray of chest of same dog following resolution of pneumonic process in the right upper lung lobe. Note disappearance of the opacity seen in the previous x-ray.

The immediate increase in hemoglobin and red blood cell count as observed by Andrus and others was substantiated by our experiments. This apparently represents the organism's effort to compensate for the lessened lung capacity. The eventual effect on the organism has not been studied thus far. It is impossible to predict accurately the possible sequelae that may occur to organs as a result of working under persistent oxygen want. The effect on the circulatory and nervous systems, metabolic organs, and kidneys that would follow such persistent anoxia might lead to irreparable retrogressive changes. All dogs apparently compensate early for lung capacity reduction, since the altered blood findings return to an average normal range within a few weeks. The oxygen and carbon dioxide content of the blood changes little.

TABLE I  
REDUCTION OF LUNG CAPACITY BY BRONCHIAL STENOSIS WITH ATELECTASIS OF THE CORRESPONDING LOBES IN SEVEN DOGS

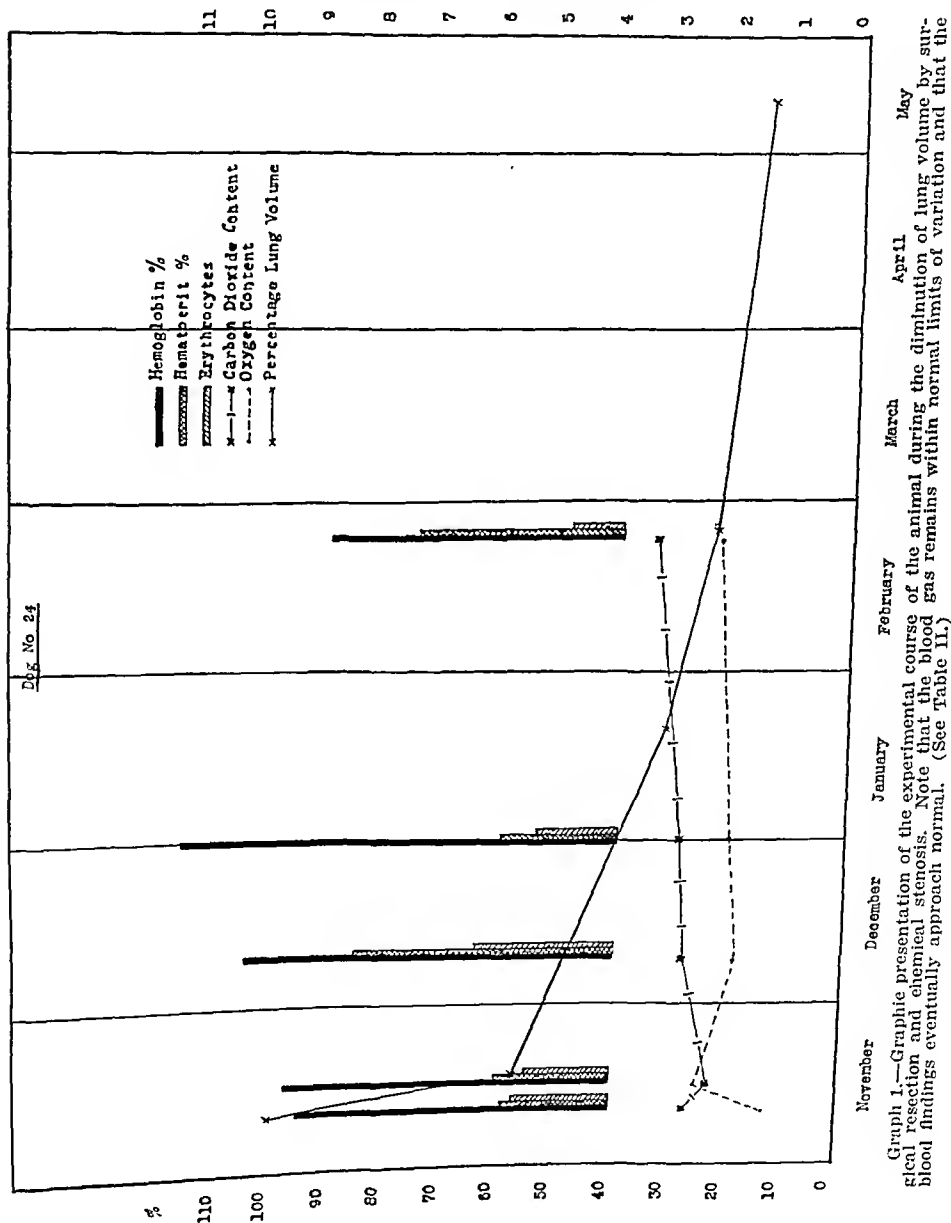
DOG	28% LEFT LOWER	15% LEFT UPPER	25% RIGHT LOWER	8.3% RIGHT ACCESSORY	8.7% RIGHT MIDDLE	15% RIGHT UPPER	REDUCTION OF LUNG (%)	RESULTS
748	Collapsed 10/18/37	Collapsed 10/18/37	Collapsed 11/1/37	Collapsed 11/1/37	Collapsed 5/14/39	Inflated	85.0	Living; normal
758	Collapsed 1/11/37	Collapsed 1/11/37	Collapsed 2/19/38	Collapsed 2/19/38	Inflated	Inflated	76.3	Had worms. Died 6/27/38; cause unknown
760	Collapsed 10/5/37	Collapsed 10/5/37	Collapsed 11/1/37	Collapsed 4/1/39	Collapsed 11/1/37	Inflated	85.0	Died 6/15/39; cause unknown
617	Collapsed 5/11/31	Inflated	Collapsed 10/29/30	Collapsed 10/29/30	Collapsed 10/29/30	Collapsed 10/29/30	85.0	Died 5/23/31; spontaneous pneumothorax
161	Inflated	Collapsed 4/29/31	Collapsed 3/4/31	Collapsed 6/10/30	Collapsed 4/29/30	Collapsed 6/10/30	72.0	Died 1/9/32; pneumonia, left lower
638	Inflated	Collapsed 12/8/30	Collapsed 5/12/31	Collapsed 6/1/30	Collapsed 5/12/31	Inflated	57.0	Sacrificed 6/15/32; normal
591	Collapsed 10/5/37	Collapsed 5/10/37	Collapsed 10/5/37	Collapsed 11/1/37	Collapsed 11/1/37	Inflated	85.0	Sacrificed 11/15/37; normal

TABLE II  
REDUCTION OF LUNG CAPACITY IN PART BY RESECTION AND IN PART BY BRONCHIAL STENOSIS WITH ATELECTASIS OF THE CORRESPONDING LOBES IN NINE DOGS

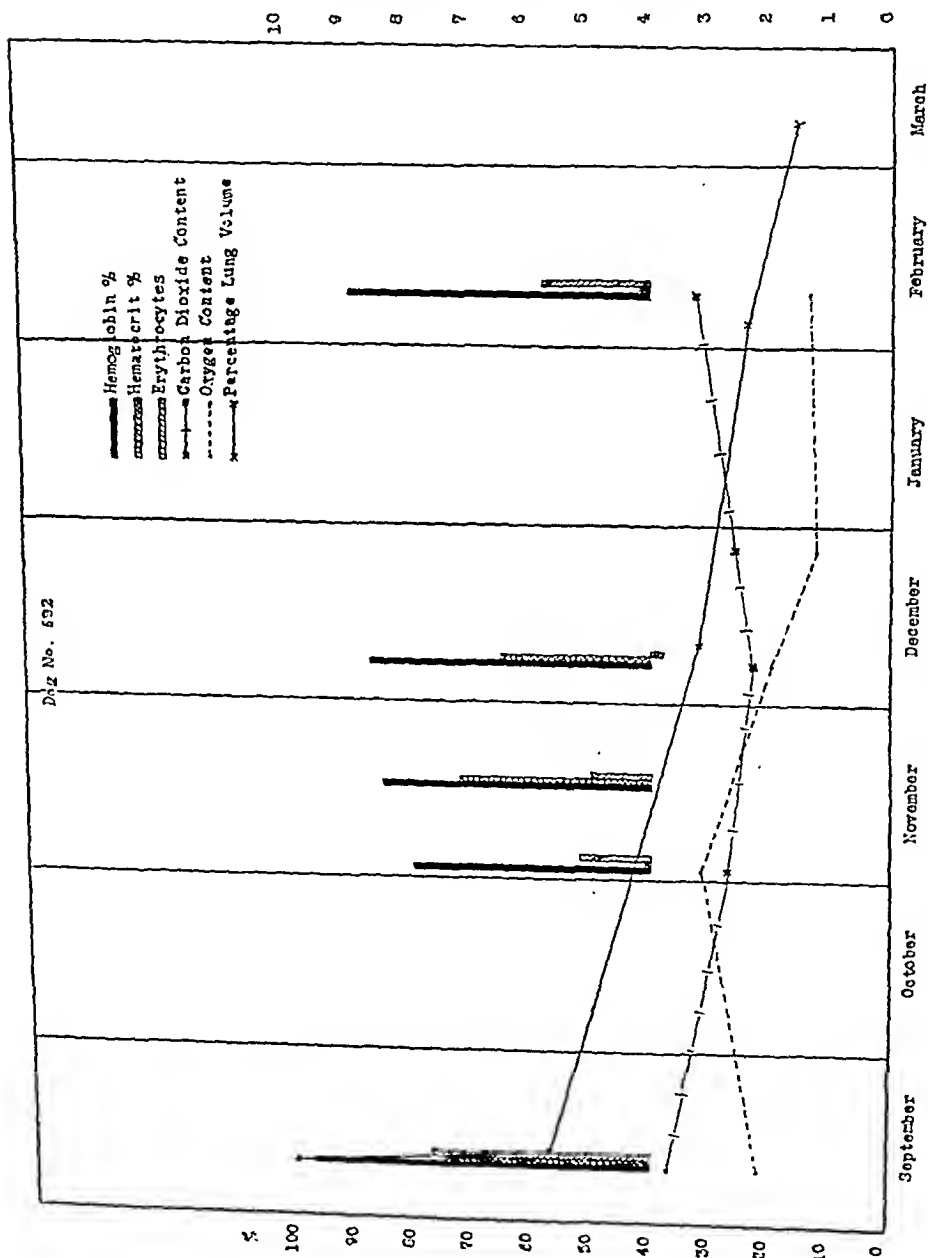
DOG	25% LEFT LOWER	15% LEFT UPPER	25% RIGHT LOWER	8.3% RIGHT ACCESSORY	8.7% RIGHT MIDDLE	15% RIGHT UPPER	REDUCTION OF LUNG (%)	RESULTS
57	Pneumonectomy 4/28/38		Collapsed 5/15/37	Collapsed 5/15/37	Collapsed 2/25/39	Inflated	85.0	Living; normal
615	Inflated		Collapsed 10/29/30 Pneumonectomy 2/19/31				43.0	Died 7/27/31; pneumonia, left lung
612	Collapsed 6/5/30 Pneumonectomy 7/1/30		Inflated	Collapsed 10/9/30 Bilobectomy 4/23/31	Collapsed 11/28/30	Inflated	60.0	Sacrificed 7/1/33; normal
795	Collapsed 10/29/30 Pneumonectomy 4/23/31		Collapsed 8/22/30 Bilobectomy 8/26/30	Collapsed 7/15/30	Inflated	Inflated	76.3	Sacrificed 7/1/33; normal
692	Pneumonectomy 9/8/38		Collapsed 12/10/38	Collapsed 2/4/39	Collapsed 3/7/39	Inflated	85.0	Died 3/8/39; spontaneous pneumothorax
24	Pneumonectomy 11/17/38		Collapsed 1/21/39	Collapsed 2/25/39	Collapsed 5/14/39	Inflated	85.0	Living; normal
25	Pneumonectomy 11/16/38		Collapsed 2/4/39	Collapsed 2/25/39	Inflated	Inflated	76.3	Sacrificed 3/18/39; infected chest wall
749	Pneumonectomy 11/11/38		Collapsed 11/4/39	Collapsed 4/1/39	Collapsed 11/4/39	Inflated	85.0	Died 11/6/39; spontaneous pneumothorax
746	Pneumonectomy 9/1/38		Collapsed 12/17/38	Inflated	Collapsed 3/18/38	Inflated	76.7	Died 4/13/39; pyothorax

This in itself would seem to indicate that the cellular increase in the blood is a compensatory measure to enhance the faculty of blood gas exchange in a lung of reduced functional capacity.

A marked shift in the mediastinal contents occurs as the lobes of the lung become completely collapsed. Additional and new stresses are put on the supporting structures of the heart and mediastinum. Without adequate time for adjustment to the new relationships, embarrass-



ment to circulation and to cardiac action is likely to transpire. The tolerance of the heart to changes of position varies somewhat with the direction of the shift. Rienhoff and others have found that in man the heart and great vessels tolerate a shift to the left better than in the opposite direction.<sup>16</sup> However, total ablation of the right lung may also result in little or no disturbance of cardiorespiratory function. A rapid change in elevation of the diaphragm may lead to dysfunction



Graph 2.—Note minimal variation in blood findings during diminution of lung volume. This animal developed spontaneous pneumothorax and died one day after lung capacity was decreased to approximately 15 per cent of normal. (See Table II.)

of the abdominal organs.<sup>17</sup> The loss of manipulatory function of the lung lobes on the thoracic veins and the ensuing continuously increased negative intrathoracic pressure may have an undetermined effect upon the return flow of blood to the heart.

When, on massive collapse of the lung lobes, the diaphragm becomes elevated to the maximum degree, either the remaining lobes must overdistend or pneumothorax must follow. Actual experience demonstrates that both frequently occur. The pneumothorax is gradually reabsorbed over a period of a few weeks as the uncollapsed lobes overinflate to fill the space previously occupied by the collapsed lobes. Even in dogs where a marked pneumothorax had persisted for several weeks following lung collapse or resection, little pleural fluid developed and no appreciable pleural thickening was grossly demonstrable. This is most probably due to the ability of the remaining inflated lung tissue to obliterate ultimately all of the pleural space. The intrapleural negative pressure following atelectasis of an entire lung was found to be altered on each side of the chest, but more so on the side of collapse (see protocol of Dog 748). The usual alteration was as follows: on the side of atelectasis, -11 to -14 cm. H<sub>2</sub>O; on the uncollapsed side, -9 to -11 cm. H<sub>2</sub>O; thus, an increased negative pressure of approximately 3 cm. H<sub>2</sub>O, or 50 per cent, on the uncollapsed side, and from 5 to 6 cm. H<sub>2</sub>O, or 85 per cent, on the side of atelectasis. This explains why the air is seen on the side of collapse when a spontaneous pneumothorax results from the collapse of one entire lung.<sup>18</sup>

Microscopic sections of the resultant overdistended pulmonary tissue reveal widespread compensatory emphysema. Although the sublethal reduction in lung capacity may be accomplished over a period of several weeks or months, marked stretching and fragmentation of the alveolar walls occur (Fig. 3B). This undoubtedly causes a decrease in respiratory efficiency of the lung tissue. As a result of the normal elasticity of lung tissue, a gradual, rather than a rapid, distention is probably more easily tolerated and with less permanent damage to the lung parenchyma. A severe injury to the lung parenchyma would necessarily result in poorer gas exchange. The eventual condition might well be compared to the lungs of a patient with marked silicosis. As a result of this increased load on the circulatory system, acute right heart damage or failure is likely to develop.

The clinical significance of the above findings may be seen in the bilateral extirpation of lung tissue in the treatment of bronchiectasis. Partial obliteration of the residual pleural space following lobectomy may be obtained by paralyzing the diaphragm. In this way overdistention of the remaining pulmonary tissue is reduced to a minimum. Whether the paralysis should be temporary or permanent and whether it should be unilateral or bilateral may be governed by the degree of

involvement, vital capacity, and other factors in each individual case. The importance of this factor will vary indirectly with the amount of atelectasis and shrinkage of the involved lung lobes prior to operation. Experimental work in this regard will appear in a later publication.

### CONCLUSIONS

1. Healthy dogs may remain well and active after reduction of volume of normal lung to 15 per cent, thus demonstrating a high degree of respiratory reserve.

2. Reduction of lung capacity is accompanied by a compensatory adjustment of the organs of cardiorespiratory function.

3. Marked compensatory emphysema, with stretching and fragmentation of the alveolar walls, occurs and persists in the remaining overdistended pulmonary tissue.

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# CLOSURE AND SUBSEQUENT CARE OF OBSTETRIC AND GYNECOLOGIC ABDOMINAL WOUND DISRUPTIONS

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WILLIAMSON<sup>20</sup> estimates 2,500,000 laparotomies are performed annually in the United States. Since evisceration through the postoperative abdominal wound occurs in approximately 0.6 per cent (based upon a combined series of reports<sup>6, 8, 9, 11, 14, 20, 22</sup>), there would be approximately 15,000 such complications yearly. The average mortality is 33 per cent in association with rupture of abdominal wounds, and thus there would be an estimated 5,000 deaths. The actual number of deaths directly attributable to the wound separations alone has not been ascertained, but, if one may assume that it ranges from one-fifth to one-half of the group, then 1,000 to 2,500 people die because of the evisceration. The morbidity and complications in the survivors add further to the gravity of this tragic condition.

The limited amount of literature gives direct and indirect causes of evisceration and offers some means of prevention, but notwithstanding these commendable publications the problem is incompletely solved. Moreover, there is a paucity of information on the care subsequent to eventration. Its infrequency allows only those connected with a large surgical service an opportunity for proper study.

This report deals with the closure and subsequent care of evisceration in obstetric and gynecologic patients, but, since the same therapeutic factors probably prevail in all laparotomy wound disruptions, these methods would seem generally applicable.

## A REVIEW OF LITERATURE

Jenkins,<sup>11</sup> at the University of Chicago, in an extensive study on all abdominal eviscerations and on suture material reports 36 cases of evisceration and reviews 1,258 others. Singleton and Blocker<sup>20</sup> have since added 61; Fallis,<sup>6</sup> 49; Glenn and Moore,<sup>8</sup> 22; Whipple and Elliott,<sup>23</sup> 6; Kraissl, Kesten, and Cimiotti,<sup>13</sup> 30; Kross,<sup>14</sup> 44; Hinton,<sup>9</sup> 19; Baer, Reis, and DeCosta,<sup>2</sup> 7; and von Graff,<sup>22</sup> 9. Thus, to date 1,505 cases of dehiscence of abdominal incisions have been reported with an average mortality of approximately 33 per cent.

Jenkins<sup>11</sup> observed an immediate mortality of 18 per cent in a pooled group of 227 obstetric and gynecologic patients. Baer, Reis, and DeCosta<sup>2</sup> had 14 per cent in 7 cases. Horner<sup>10</sup> had no immediate deaths in 3 cases, but 1 patient succumbed at the time of herniotomy two years

later. Even with the 65.5 per cent death rate in Singleton and Blocker's<sup>20</sup> patients, the pooled data support the contention that the lower abdominal gynecologic and obstetric incisions are associated with a lower mortality in the event of disruption.

Various explanations for evisceration include sudden and undue strain upon the incompletely healed wound, infection in the wound, inadequate hemostasis, abdominal distention, incorrect approximation of tissues, abnormal wound healing, constitutional disorders, and possibly sensitization to suture material.

In 1925 Shipley<sup>19</sup> recommended for the secondary closure a through-and-through silver wire suture with a pack below the wire to protect the viscera and a pack above to keep the edges apart. After a few days, when the wound edges are healthy, both packs are removed; the sutures are then further tightened and a small gauze pack is placed again in the superficial portion of the wound for about ten days more. The skin edges are closed after this pack is removed. Thus, some fifteen to twenty days elapse after the evisceration before the wound is completely closed.

Eliason and McLaughlin<sup>5</sup> recommend packing of the wound and fixation by adhesive tape. The exception to this routine is made only for those in very good condition. Pool<sup>18</sup> uses a Mikuliez tampon when suturing is not feasible. Starr and Nason<sup>21</sup> concur with Pool in the employment of aspiration of the bowel if it cannot be otherwise replaced, while Horner<sup>10</sup> once sutured a rubber dam to the skin edge to protect the protruding viscera.

On the contrary, Bellin,<sup>3</sup> Milbert,<sup>17</sup> Starr and Nason,<sup>21</sup> Bevan,<sup>4</sup> Koster and Kasman,<sup>12</sup> White,<sup>24</sup> Meleney and Howes,<sup>16</sup> and Maes, Boyce, and McPettridge<sup>15</sup> agree ordinarily upon immediate secondary closure and generally subscribe to the use of mass through-and-through sutures of nonabsorbable material. The trend is definitely away from the use of absorbable sutures for the approximation of the peritoneum. Practically all agree upon wound packing and adhesive bandage for the patient in extremis, completing the closure when the patient's condition improves sufficiently.

#### DATA

On the obstetric and gynecologic services at the University of Chicago Clinics there have been 3,179 (Table I) abdominal operations up to June 30, 1939. The service started in October, 1929, at the Albert Merritt Billings Hospital, and in May, 1931, at the new Chicago Lying-in Hospital. Seven disruptions of the abdominal wound occurred in the 1,370 laparotomies in obstetric patients which gave an incidence of 0.51 (0.510) per cent. In the gynecologic group of 1,809 it occurred 8 times, an incidence of 0.44 (0.442) per cent. The total of 3,179 operations and 15 eviscerations makes the rate 0.47 (0.468) per cent. This is somewhat higher than several reports, yet it comes well within the average of range

of the current literature. These patients have been for the most part staff cases (teaching service) and evisceration has occurred on the services of all attending men. The primary closures in all 15 cases of evisceration were made with catgut suture for peritoneum and fascia. Eight had three silkworm gut tension sutures and 1 had two such sutures. The skin edges were closed in 5 with skin clips, in 7 with silk, and in 3 with catgut. Three patients had wound separation with tension sutures in situ. In retrospect it would seem that the small number of supporting nonabsorbable sutures were inadequate.

TABLE I

TYPE OF OBSTETRIC AND GYNECOLOGIC ABDOMINAL OPERATIONS AND INCIDENCE OF EVISCERATIONS\*

	OPERATIONS	NO. OF EVISCERATIONS	
		NO.	PER CENT
<i>Obstetric</i>			
Cesarean section	1162	5	
Hysterotomy and hysterectomy (therapeutic abortion)	80	1	
Removal of ruptured uterus	15	0	
Salpingectomy (ectopic)	42	0	
Postpartum abdominal sterilizations	71	1	
Total	1370	7	0.51
<i>Gynecologic</i>			
Adnexal operations	445	4	†
Hysterectomy			
Complete	333	2	‡
Incomplete	821	2	
Myomectomy	46	0	
Exploratory laparotomy	102	0	
Combined laparotomy and plastic	62	0	
Total	1809	8	0.442
Grand Total	3179	15	0.468

\*Mortality: immediate and delayed, 13.33%; immediate, 6.66%.

†Died on third day (1 patient).

‡Death after elective herniotomy five months later (1 patient).

The type of primary operations are listed in Table I. Hysterotomy and hysterectomy for therapeutic termination of pregnancy before the period of viability is listed separately from hysterotomy after viability (cesarean section), although there is probably little occasion for such differentiation. The removal of ruptured uteri (post partum) is given special attention because all of these patients had been delivered by the vaginal route and because several had been delivered outside the hospital by other agencies. "Post-partum abdominal sterilization" means that group of patients in which the abdomen was opened in six to thirty hours after vaginal delivery for the ligation of the tubes, a procedure recently reported by Adair and Brown.<sup>1</sup> The one disruption in this subgroup took place in an atelectatic patient who had been placed on "blow bottles." No deaths followed evisceration in the obstetric series.

Adnexal operations include those procedures in which the ovaries, tubes, and/or ligaments were treated. The heading of hysterectomy includes all uteri removed with or without the adnexa. Exploratory laparotomies include those not under other headings, as freeing intestinal obstruction, biopsy of pelvic structure, and closure without removal of viscera, etc. The combined laparotomy and plastic operations refer to those in which both abdominal and vaginal operations were performed concurrently.

The first of the 2 deaths in the gynecologic series occurred from a generalized peritonitis four days after the secondary closure of the wound. At the primary operation two large ovarian cysts were removed. This patient took a poor anesthesia apparently because of previous injury to the laryngeal nerve during a thyroidectomy and a tracheotomy was performed after the operation to maintain an airway.

Another patient who had recovered from the evisceration returned five months later for an elective repair of the resultant hernia but succumbed eighty-three days later from agranulocytosis and infection. This patient had originally had a total hysterectomy and removal of the adnexa for uterine carcinoma. Between the first and second operations she had a complete series of deep x-ray treatments.

Thus, 2 deaths followed evisceration, one directly and the other indirectly. Whether the second death should be charged entirely to the evisceration may be debated. The immediate and remote mortality rate for these 15 disruptions is 13.3 per cent. The immediate death rate alone becomes 6.6 per cent. These rates are far below the general average of 33 per cent with ranges from 0 per cent (Starr and Nason) in 15 cases to 63 per cent (Glasser) in 8 cases.

All eviscerations are listed in Table II. At the primary operation the first 3 obstetric patients had local and gas anesthesia; the next 3 had local only, while the last (seventh) one had spinal. On the other hand, all of the gynecologic group were given combined ethylene and ether anesthesia. The various contributory factors for evisceration were distention, coughing, vomiting, or other undue stress upon the incompletely healed wound. Six cases had been operated previously. The wide age range, various clinical conditions, and different primary operations exclude single factors as outstandingly important in contributing to evisceration. However, a suprapubic midline incision was used in all these cases.

The first, second, and third obstetric patients and the third, fourth, and sixth gynecologic patients had had previous operations.

Eight of the 15 patients had serosanguineous discharge before disruption, while 7 were without premonitory signs. The dehiscences were recognized promptly and all patients were treated by immediate surgical closure of the wound. Six of the 15 were reclosed by catgut suture layer by layer throughout and in 1 of these wire tension sutures were used. These, with 2 exceptions, were the earlier cases. Two pa-

TABLE II  
CONDENSED REPORT OF CASES

UNIT NO.	AGE	PRIMARY		PREMONI- TORY SIGNS	SECONDARY CLOSURE		
		DIAGNOSIS	OPERATION		METHOD*	ANESTHESIA	RESULTS
<i>Obstetric</i>							
1. No. 133461	20	Contracted pelvis	Laparotrachelotomy, sterili- zation	Yes	S.W.*	Local	Recovery
2. No. 210892	25	Previous section	Laparotrachelotomy, sterili- zation	Yes	S.W.	Gas	Recovery
3. No. 79296	30	Contracted pelvis, postoper- ative hernia	Porro section, herniotomy	No	C.G.	Gas	Recovery
4. No. 141605	33	Multiparity, varicose veins	24 hr. sterilization, left oophorectomy	No	C.G. & S.W.	Morphine & scopolamine	Recovery
5. No. 84293	34	Contracted pelvis	Laparotrachelotomy	No	S.W.	Local	Herniotomy later
6. No. 110050	34	Contracted pelvis, umbilical hernia	Laparotrachelotomy, herni- otomy	Unrecorded	S.W.	Gas	Recovery? Hernia
7. No. 141204	39	Pulmonary tuberculosis (6 weeks pregnant)	Hysterectomy	No	C.G. & W.	Local	Recovery
<i>Gynecologic</i>							
1. No. 38507	21	Ovarian cyst	Oophorectomy, appendec- tomy, suspension	No	C.G. & S.W.	Gas	Recovery
2. No. 57884	32	Mitral stenosis, anemia, cystocele, rectocele	Supracervical hysterectomy	Yes	C.G.	Gas	Recovery
3. No. 70665	34	Intestinal obstruction (postoperative)	Release of adhesion	Yes	S.W.	Local	Recovery
4. No. 83590	41	Fibromyomas	Total hysterectomy	Yes	S.W.	Gas	Recovery
5. No. 179213	43	Fibromyomas	Salpingo-oophorectomy	Yes	S.W.	Gas	Recovery
6. No. 131069	45	Ovarian cyst	Supracervical hysterectomy Bilateral salpingo- oophorectomy	Yes	C.G.	Local	Death on fourth day
7. No. 76746	49	Fibromyomas	Supracervical hysterectomy	No	C.G.	Gas	Recovery
8. No. 40326	65	Obesity, carcinoma of corpus	Total hysterectomy, bilat- eral salpingo-oophorec- tomy	No	C.G.	Gas	Recovery, hernia
*S.W., Silkworm gut through-and-through looped suture. C.G., Catgut suture.							

\*S.W., Silkworm gut through-and-through looped suture;  
C.G., Catgut layer by layer;  
C.G. & S.W., Catgut on peritoneum and silkworm gut mass suture;  
C.G. & W., Catgut and silver wire.

tients had closure of the peritoneum with absorbable material, while the remaining portion of the broken-down area was reapproximated by silkworm gut sutures. The remaining 7 were treated by mass through-and-through "looped" or partial figure-of-8 suture of silkworm gut. One patient in each of these three types of secondary closures developed a postoperative hernia.

#### PROCEDURE

It is universally agreed that early recognition of this complication is imperative. Even with a well-organized intern and resident staff the significance of a sudden discharge of serous or sanguineous fluid from the wound may be overlooked. On the other hand many put so much stress upon the importance of this sign that perhaps a word of caution is apropos. Admittedly, careful scrutiny is an excellent policy, but one should not invade the wound unless additional evidence warrants it.

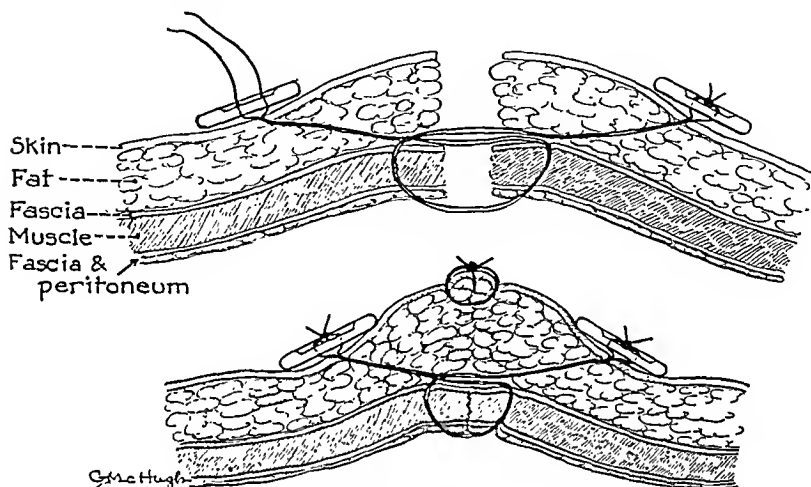
The bowel or omentum is recognized easily in the opened incision, but identification of bowel wall or omental edge through a slight aperture in the skin is more difficult. In the incomplete evisceration superficial tympany within the wound ordinarily indicates the presence of bowel. There may be localization of distress in the wound in connection with symptoms of intestinal obstruction. Some wounds break down relatively asymptotically and the condition is not discovered until the dressings are removed. Often the patient is aware of a sudden "giving away" or loss of support of the abdominal wall.

When the condition is discovered, the dressings are reapplied without changing and held in place by the adhesive corselette. The patient is told that the edge of the wound has separated slightly and that now is the best time to reapproximate it. Great pains are taken to avoid excitement. The patient is given morphine and scopolamine and is taken in her bed to the operating room when everything is in readiness. The operator again reassures the patient and suggests that perhaps a few "whiffs" or "breaths" of gas will make it easier for her. When the surgical team is scrubbed, gowned, and ready, the anesthetist begins the anesthesia. The proponents of local anesthesia advocate it to safeguard further visceral extrusion; still some would hesitate to use infiltration in the presence of infection. The advantages of gas are that it shortens the time of the closure, enhances relaxation, and permits any necessary manipulation. One patient in this series whose condition was particularly serious relaxed very well with "twilight sleep" alone.

After the patient is well anesthetized, an unscrubbed member of the team removes the adhesive corselette. The skin is prepared with tincture of iodine and alcohol applications: particular care is exercised to keep these solutions from contacting the bowel and omentum. If there is no accentuation of the evisceration, the external sutures may be removed before preparation of the skin; otherwise their removal follows the preparation and draping. Moist warm laparotomy pads may be used to prevent further protrusion. The viscera are freed from the wound

edges only and replaced with the least possible manipulation and exploration. Further intra-abdominal exploration should be avoided as it favors the spread of infections.

In this series the mass "looped" or partial figure-of-8 suture of silk-worm gut was employed seven times (Figs. 1 and 2). The only two deaths occurred in those closed secondarily with absorbable suture. Yet from the nature of the cases it is obvious that neither the method nor suture material was a responsible factor in the fatalities.



### Sutures tied - Closure completed

Fig. 1.—Cross section of "loop and a half" mass sutures.

This stitch is a modified figure-of-8, lacking the top of the superficial loop. Without a better designation it is termed a "loop and a half" or a "through-and-through looped" suture. To facilitate understanding of this procedure, it is described as follows. Two strands of silkworm gut are tied over a button. The two free ends are then threaded on a large cutting needle. The suture is started 6 to 7.5 cm. ( $2\frac{1}{2}$  to 3 inches) from the wound edge and brought out just external to the fascia. It is then carried across the wound to the opposite side, down through the fascia and muscle, and out through the peritoneum near the edge of the wound. (In executing this part the sutures should pierce the healthy fascia some distance lateral to the wound edge.) The needle is then carried back to the original side and carried up through the peritoneum, muscle, and fascia, and thence across the wound and out through fat and skin, ending 6 to 7.5 cm. from the wound on the opposite side. These free ends are then threaded through a button and held until all the sutures are placed. A large number of sutures may be necessary for they should be placed not more than 1.5 to 2.5 cm. ( $\frac{3}{4}$  to 1 inch) apart.

If the wound is uninfected and one fears skin contamination, one may place the deep loop first. Under these circumstances the stitch is started in the fascia making the deep loop, coming out through the fascia on the opposite side, and ending by coming out through the skin on the original side of the wound. The other two ends of the suture are then threaded on the needle and brought out through the skin on the opposite side. These free ends are threaded through the button and held.

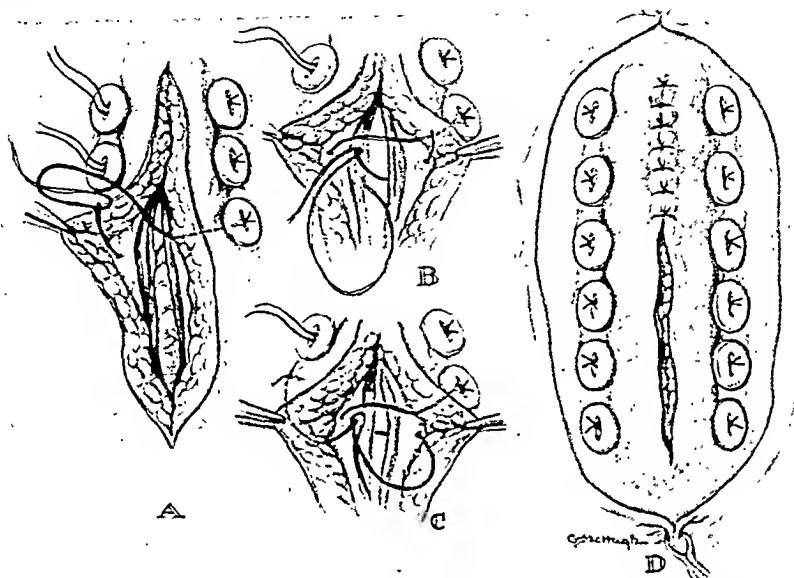


Fig. 2.—Drawing of method of secondary wound closure by "loop and a half" mass sutures.

After all the sutures are placed, steady traction on their free ends closes the wound completely. The greatest care is exercised in closing the wound to keep it free from viscera or omentum and to obtain proper apposition of the layers.

This suture method fulfills the requirements of the generally accepted principles of treatment. Furthermore, one effects a more accurate and correct apposition of the peritoneum, muscle, and fascia respectively than with the usual mass through-and-through suture. Indicated superficial drainage may be easily instituted without disturbing the approximation of the deeper layers.

By proper fixation with the through-and-through "looped" suture the skin edges need only to be brought together. This may be done with silk or skin clips. The usual dry dressings are applied and held firmly in place.

Strict peritonitis therapy is continued for the next three days even in the absence of infection and, if at that time the patient's condition justifies, this management is gradually discontinued. As soon as the

patient has been returned to her room 1,000 to 2,000 c.c. of physiologic sodium chloride or Ringer's solution is given subcutaneously. The amount depends upon the patient's need for fluid and the rate of its absorption. Some six to twelve hours later 1,000 to 1,500 c.c. of 10 per cent glucose is administered intravenously over a period of one to one and one-half hours. Its diuretic action is avoided considerably by its slow administration. At least a total of 3,000 c.c. of Ringer's, Hartman's, or sodium chloride and glucose solutions must be given daily. Five per cent glucose solution may be given subcutaneously but ordinarily only when the intravenous route is contraindicated. Each morning 1,000 to 1,500 c.c. of subcutaneous fluid is administered and then in the afternoon the intravenous solution is started, after which more saline solution may be given subcutaneously. Deviations in the amount of fluids and concentrations of the glucose should be made entirely upon direct indication. This process is repeated daily until the patient's condition becomes favorable for oral administration. The subcutaneous sites are usually the thighs because this location will not interfere with respiration. The rectal route is used seldom because one of the intentions in the therapy is to keep the bowel at rest. Water may be used to moisten the lips and the mouth, but it should not be swallowed.

At the first signs of vomiting or upper abdominal distention gastric siphonage should be instituted by the Wangenstein<sup>25</sup> method. This apparatus, of course, should be watched carefully to insure its proper functioning. The amount of gastric fluid lost is carefully noted and an equal amount of isotonic sodium chloride solution is given to the patient to maintain a chloride balance. The small gastric tube which is passed through one of the nasal cavities may be left in situ for many hours before it is removed. After the patient is rested, it may be inserted again. This process may be repeated as long as necessary. It is important to keep an accurate record of fluid intake and output. Should the patient perspire freely or otherwise lose more fluids than usual, dehydration must be avoided by increasing the amount of parenteral fluids. Distention of the lower bowel may be relieved by the use of rectal tube or glass dumbbell. The patient is kept in a quiet room in Fowler's position and receives special nursing attention. Visitors are restricted to prevent fatiguing and exhausting the patient. Sedatives and analgesics are used freely but judiciously.

One or more transfusions are indicated if there is an anemia. If peritonitis actually occurs, small frequent transfusions may be important, even in the absence of anemia.

Appropriate therapy is instituted for other complications when they arise.

Chemotherapeutic agents, such as sulfanilamide and sulfapyridine, are indicated only when the infectious bacteria are affected bacteriostatically or bactericidally by these medicaments. The value of these prepara-

tions is related directly to their timely and judicious administrations and proper dosage.

If by the end of seventy-two hours absence of evidence of peritonitis persists, as determined by clinical and laboratory means, the patient may be started on clear nonfermenting fluids by mouth. Otherwise the peritonitis therapy is continued until she improves enough to be given oral fluids. Liquids by mouth are given in units of 15 to 30 c.c. ( $\frac{1}{2}$  to 1 ounce) at fifteen-minute intervals. The amount is increased gradually over the next several hours. The fluids and foods are increased in amount and character as rapidly as the patient tolerates them. Within the next few to several days, the patient arrives back on a maintenance diet. Should evidence of intolerance occur, the diet should be arrested and adequate fluids given parenterally.

The mass sutures are left for ten days or longer, and then only the alternate ones are removed. This is done by raising every other button on one side and cutting the suture. These are more easily removed the following day. A day or so later the process is repeated with the remaining sutures and finally the skin clips or silk is removed.

The success in this therapy of abdominal disruption depends upon early and prompt recognition of the condition, replacement of the viscera without additional soiling of the peritoneal cavity, minimal manipulation, and the adequate administration of the present-day therapy for peritonitis in all cases even in the absence of clinical peritonitis.

#### SUMMARY AND CONCLUSIONS

If there are 1,000 to 2,500 deaths annually in 15,000 estimated eviscerations, certainly the focusing of attention upon this complication is justified. The current literature stresses the causes and prevention of evisceration, yet very little deals with the subsequent treatment. Some of the points in prevention are gentleness in care of tissue, adequate hemostasis, accuracy, and thoroughness in closure of the various layers of the abdominal wall, the intelligent and judicious use of suture materials and the elimination and prevention of undue and sudden stresses as coughing, vomiting, distention, and unreasonable exercise.

When evisceration does occur the following will enhance recovery and reduce morbidity:

1. Early recognition of premonitory signs and actual evisceration.
2. Immediate closure with nonabsorbable mass suture with minimal manipulation.
3. Employment of wound pack only for the very critically ill.
4. Drainage only on positive indications.
5. Strict peritonitis care.

The employment of through-and-through "looped" or "loop and one-half" mass nonabsorbable suture is recommended for closure of evisceration. This method, along with strict medical management for potential or actual peritonitis, has, in this limited series, yielded good results. It

is in agreement with and amplifies recent reports. It does not interfere with drainage of the superficial portion of the wound and drainage from the peritoneal cavity can be instituted by the proper placement of the sutures. At the same time this approximation of tissues gives full vision to the wound edges and appears to give better apposition of the peritoneum, muscle, and fascia respectively than the usual through-and-through mass suture. Current reports advise against the employment of absorbable suture material in secondary closures.

Surely this type of closure has been used by others, but thus far not one report has been found under titles referable to abdominal wound disruptions.

Acknowledgment is made to Dr. Fred L. Adair and the various members of his staff for their cooperation in this study.

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## EXPERIMENTAL STUDIES WITH SYNTHETIC FIBER (NYLON\*) AS A BURIED SUTURE

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SUTURE material has presented a problem to surgeons ever since its inception. The use of nonabsorbable suture has given way to the absorbable suture and again the use of nonabsorbable material is becoming popular. Suture material must approximate tissues and keep them in the desired position until they have united. The suture should not introduce infection or cause irritation in the tissues in which it is used. Since nonabsorbable material is encapsulated and walled-off as a foreign body, the smaller the diameter of the material used, the less will be the tissue response and the greater the ease in encapsulating it. Thus, a fine nonabsorbable suture with a tensile strength greater than an absorbable suture (of even wider diameter) would be advantageous.

Catgut is known to be irritating to the tissues,<sup>1</sup> calling forth an early leucocytic response. Chromicized catgut is less irritating than non-chromicized gut and silk causes even less irritation than any type of catgut. The tensile strength of silk is greater than that of catgut of equal diameter. Silk allows tissue fluids and serum to penetrate between its twisted strands which is followed by an infiltration of leucocytes and granulations within the interstices of the fibers and is followed by an invasion of fibroblasts. Silk treated to prevent this penetration is more irritating to the tissue and is rather stiff and wiry unless soaked before using. When wet, it is more difficult to handle and gnarls or twists into knots. Much of the elasticity of the silk is also lost in this treating process.

We wish to present the results of investigative work on a new synthetic fiber which has practically none of the disadvantages of catgut and has several improvements over silk.

Nylon<sup>2</sup> is a fiber material composed of a synthetic polymer derived from the chemical union of a diprimary diamine and a dicarboxylic acid. It is a chemically inert substance and will thus withstand repeated steam and chemical sterilizations without deterioration. The suture is insensitive to aqueous solutions, except strong acids. The x-ray diffraction pattern has placed this filament in the class of true fibers. Being a synthetic chemical fiber, the material is not subject to inherent bacterial contamination as are sutures derived from tissues of animals or living organisms.

The suture is made in various sizes from No. 000 to No. 2 twisted and from No. 000 to No. 2 braided. The monolithic strand comes in

\*The materials used in these experiments were furnished by Curity Laboratories of the Lewis Mfg. Co., Walpole, Mass.

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is in agreement with and amplifies recent reports. It does not interfere with drainage of the superficial portion of the wound and drainage from the peritoneal cavity can be instituted by the proper placement of the sutures. At the same time this approximation of tissues gives full vision to the wound edges and appears to give better apposition of the peritoneum, muscle, and fascia respectively than the usual through-and-through mass suture. Current reports advise against the employment of absorbable suture material in secondary closures.

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eight-day animals. Those sacrificed after fifty-six days presented no infiltration and a definite ring of fibroblasts walling off the suture (Fig. 1).

Microscopic sections of twisted nylon presented a few leucocytes about the suture. The twenty-eight-day animals had lymphocytes in some sections. Later examinations of the nylon revealed the material well walled off from the tissue with no reaction about it.

Microscopic study of the dyed and undyed silk revealed a tissue reaction not appreciated on gross examination. The silk in the fascia and muscle was infiltrated by leucocytes and surrounded by a cuff of leucocytes. The tissue of animals sacrificed after thirty-five to fifty-six days presented fewer cells about the silk and they were lymphocytes and plasma cells in place of the early leucocytic response. In one field the silk and nylon were lying within 15 mm. of each other, the nylon

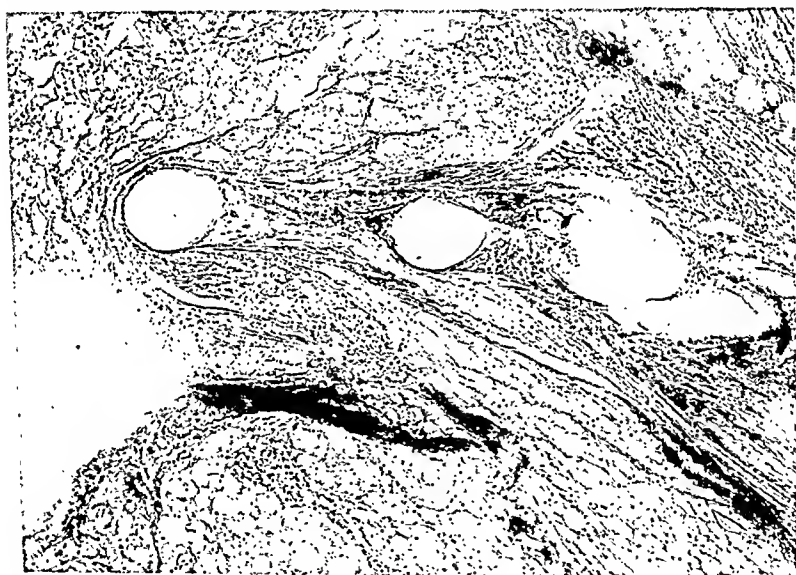


Fig. 1.—Photomicrograph of cross section of rectus muscle in which monolithic No. 000 nylon was allowed to remain for fifty-six days. There are two homogeneous segments of suture visible in the tissue surrounded by connective tissue and a few lymphocytes. ( $\times 57$ .)

free of cells and the silk infiltrated with round cells. Sections of nylon of larger diameter, No. 0, had lymphocytes and round cells in very small numbers between the fibers of the twisted filament. This was less in amount than that caused by the silk.

Twisted nylon, No. 000, is the easiest size to handle and causes less irritation than the same size silk. It is a little more irritating than monolithic nylon, however. Monolithic nylon is not as flexible as the twisted fiber, and thus forms large knots which are not well encapsulated by the tissues.

sizes Nos. 000 to 2, but it is not as flexible as the multifilament strand. Monolithic strand threaded on a needle forms a large loop over the eye, thus cutting holes when drawn through the tissues. The swaged needle has obviated this difficulty, but the suture material still cuts through when approximating soft, delicate tissues. The twisted strand has a greater tensile strength than an equal-sized strand of silk and is easier to handle for the following reasons: The end does not fray readily when cut and can be threaded with ease; when wet it does not snag or twist into knots, even with the No. 000 gauge; there is an ease in approximating tissues without breaking the suture because of its elasticity which also prevents slipping of the knots, and a very small space is occupied by three knots.

#### PURPOSE OF EXPERIMENT

The following experiments were performed on dogs using nylon and silk to determine the tissue response, the irritative phenomena, the ability of the material to hold under tension, foreign body reaction in delayed healing by the introduction of infection, and the tendency of the material to form fistulous tracts.

Eighteen fascial experiments were carried out on nine dogs. Left and right 4-inch paramedian abdominal incisions were made in the skin of each dog. The anterior rectus sheath was incised for 1 inch at the upper and lower ends of the incision, leaving a 2-inch intact anterior rectus sheath. The upper right rectus muscle and fascial sheath were sutured with No. 000 monolithic undyed nylon, the lower right muscle and fascia with No. 000 twisted nylon. The left abdominal incision was made in the same manner, but the upper right rectus muscle and fascia were sutured with No. 000 undyed silk while in the lower rectus muscle and fascia, black silk was inserted.

Dogs were sacrificed at intervals of from fourteen to sixty-one days. The following gross findings were evident: The monolithic nylon, whether dyed or undyed, presented no adhesions to the overlying subcutaneous tissue. There was no collection of serum and the suture material was more flexible than when placed in the fascia. The material retained its shape and color and was not fragmented. The variation in time from twenty-eight to sixty-one days made very little difference in the gross appearance of the nylon, whether dyed or undyed. The encapsulation of the silk was more complete so that little or no silk was visible. Even the knots were covered with dense tissue. The animals sacrificed at the end of seven to eight weeks were so well healed that it was only the markers left in the tissue that helped reveal the presence of the nylon and silk.

Microscopic sections through the monolithic sutures revealed the material to be well encapsulated. There were a few lymphocytes about the suture in the fourteen-day animals and round cells in the twenty-

suture in the serosal layer was surrounded by a few cells and only occasionally was there an infiltration of the interstices of the suture filament. Two anastomoses high in the jejunum presented practically no tissue reaction on microscopic study. It is well to note here that anastomoses made by continuous suture using a nonabsorbable suture material are dangerous. The lumen of the bowel cannot dilate due to the limited elasticity of the suture and will continue to contract with healing and scarring, thus narrowing the stoma. Since this material does not fragment or weaken, one should use interrupted stitches to allow dilation of the lumen.

Microscopic examination of the blood vessels in the mesentery tied with nylon revealed complete obliteration of the artery and vein with no evidence of leucocytic or lymphocytic infiltration about the suture material. There was no evidence of the suture having cut through the tissue.



Fig. 2.—Photomicrograph of a cross section of segment of jejunum in which an end-to-end anastomosis had been performed twenty-eight days before using No. 000 twisted nylon suture. Note the absence of cells between the interstices of the twisted strand. ( $\times 100$ .)

The following experiments were performed on the stomach: A longitudinal incision was made through the anterior surface of the stomach 3 inches long; the proximal one-half of the gastrotomy was sutured with twisted black silk and the distal half with nylon, No. 000. Two layers of interrupted suture were used, followed by a peritonealizing layer of silk and nylon, respectively. The animals were examined in fourteen, twenty-one, and twenty-eight days. The incisions were healed. There was no evidence of cutting through the tissues and the mucosa was smooth and intact. Grossly, one could not differentiate the type of suture used, but on microscopic examination the silk suture was

Three-inch segments of the jejunum and ileum of seven dogs were attached to the anterior parietal peritoneum with No. 000 monolithic nylon swedged on needles to determine whether or not the bowel would cut away from the peritoneal attachment. The suture material had to be swedged on needles to prevent the formation of large holes in the seromuscular layer of the bowel when the monolithic suture looped in a large arc through the eye of the needle. Because of the poor flexibility of the suture, it would partially cut through the bowel wall when an attempt was made to approximate the bowel to the parietal peritoneum. The use of No. 000 multifilament nylon allowed for the use of fine-eyed needles and the accurate approximation of tissues without the suture material looping out between the sutures as in the monolithic strands.

Examination of the fixed loops of bowel at intervals up to sixty days revealed incomplete approximation of the bowel to the peritoneum of the abdominal wall where monolithic strands had been used. A thin, shiny mesothelial layer covered the projecting loops of suture. The bowel sutured with multifilament nylon was well approximated and no suture material was visible. The peritoneum did not reveal irritation and on cross section the material was well encapsulated. Microscopic examination of the peritoneum and bowel wall revealed the suture with a few round cells about the area, not enough to form a single layered cuff about the periphery of the suture material.

Five end-to-end anastomoses were performed on the jejunum and ileum of five dogs using No. 000 nylon sutures. The vessels in the mesentery were ligated separately for study of the effective obliteration of vessels. The usual continuous suture was placed through the full thickness of the bowel using a Connell suture on the anterior surface. A second layer of continuous Lembert suture was inserted in the serosa which approximated easily. No suture material was visible about the anastomosis. The animals were allowed fluid by mouth after six hours if they would take it, and most dogs drank freely the following day. Examination of the anastomoses at intervals from fifteen to sixty-one days did not reveal any evidence of leakage or peritonitis in any of the dogs. It was difficult to find the anastomosis after the fifth week as the suture line was so well approximated. Upon opening into the lumen, the mucosa was smooth and the suture line was not discernible. There was no evidence of the knots of suture material.

Sections of tissue from the wall of the jejunum and ileum revealed the mucosa to be well approximated, the suture material in place and no evidence of serum about it. Microscopic study of the suture in the mucosa indicated an increase in the number of round cells normally present in the mucosa, but no collar of leucocytes about the suture, as was evident with catgut. The suture in the submucous layer (Fig. 2) was surrounded by fibroblasts and connective tissue and was free of invading round cells or leucocytes in twenty-eight-day sections. The

in position presented areas of inflammation which on microscopic examination were found to be surrounded by cuffs of leucocytes six to eight rows deep. The areas where the sutures had fallen out were being invaded by fibrous tissue. Sutures in the fascia and peritoneum were well encapsulated with no evidence of leakage or fistula formation about the exposed bowel. Microscopic examination of the fascial and peritoneal attachments presented a slight round-cell infiltration about the suture but no infiltration between the fibers. The suture through the mucosa was surrounded by the normal number of round cells of the mucosa.

The following experiments were performed on the bladders of two dogs to determine fistula formation with No. 000 nylon. Through a paramedian incision in the male dog, the urinary bladder was brought up to the anterior abdominal wall. A 1-inch incision was made in the fundus of the bladder and urine escaped. The defect was sutured with two layers of interrupted No. 000 nylon and followed by a continuous suture in the serosa. The bladder was then anchored to the abdominal wound with stay sutures. The peritoneum, fascia, and skin were sutured to the wall of the bladder respectively. The wound became edematous and pink, but this subsided after ten days. The animals were sacrificed after fourteen to twenty-one days. No pus was present in the wound. There was no evidence of fistulas when the bladder was injected with colored fluid under pressure. The bladder was well healed. The serosal surface was adherent to the abdominal scar and the mucosa covered the suture line within the bladder so that it was found only by the serosal markings. Microscopic examination through the suture line to the abdominal wall revealed the suture surrounded by a single layer of cells in the fascia and scattered round cells in the subserosa of the bladder. The areas with leucocytes in the fascia were well surrounded by fibrous tissue and securely walled off. There were no invading cells in the mucosa of the bladder. The suture remained unchanged (Fig. 4).

To determine the fate of silk and nylon in infected wounds, right and left longitudinal paramedian incisions were made through the skin, anterior rectus sheath, and rectus muscle. Into the upper half of each rectus muscle four interrupted nylon sutures were placed and into the lower half of each rectus muscle No. 000 silk was inserted. The fascia was closed with interrupted nylon in the upper half and No. 000 silk in the lower. The wound on the left was inoculated with a pure broth culture of *Bacillus coli* and the right wound with a pure broth culture of *Staphylococcus aureus*. The skin was closed with No. 000 nylon.

Examination of the left wound in three dogs revealed a marked infection with edema and redness of the edges and the presence of frank pus appearing through the skin suture holes. The right wound was edematous and red; little pus was present. After fourteen days the inflammation in the left wound began to subside and the pus was less in

invaded and surrounded by a cuff of round cells. There were a few round cells about the nylon suture, but no cells in the interstices of the fiber (Fig. 3). The lack of reacting cells is striking as grossly the silk and nylon appeared identical.

Two gastroenterostomies were performed in the routine manner using continuous suture of No. 000 nylon. No suture was visible at the completion of the operations. Animals were given fluids after six hours and fed after forty-eight hours. Examination of the anastomoses after twenty-one and twenty-eight days revealed a good functioning enterostomy without adhesions. The size of the stoma was limited by the continuous suture which could not be dilated. The microscopie sections revealed a few round cells about the suture but less irritation than was present in the experimental animals in which silk was used.



Fig. 3.—Photomicrograph of a segment of stomach in which a gastrotomy had been performed twenty-one days before the upper cross section of No. 000 nylon revealed the presence of a few invading cells. The crescentic longitudinal segment of silk No. 00 on the right is invaded and surrounded by lymphocytes. ( $\times 45$ .)

The sigmoid colon of two dogs was brought up to the abdominal wall and sutured with interrupted No. 000 nylon as a colostomy. Interrupted sutures were placed between the bowel and peritoneum, second between the bowel and fascia, and then between the bowel and skin. The sutures were deliberately placed through the full thickness of the sigmoid to try to form fistulous tracts. The bowel was not opened so that if fistulas developed they could be easily found. Examination of the wound revealed puffiness and edema about the skin margins which subsided after fourteen days. The sutures cut through the skin margins in several places where the tension was great. After twenty-one days the inflammation subsided and the wound appeared pink. The dogs were sacrificed at twenty-eight days. The skin sutures remaining

dropped back into its original position. Examination after three and four weeks revealed adhesions present about the suture line which were easily freed. The suture was well covered with fibrous tissue. On cross section the suture was visualized about the nerve bundles. On microscopic examination there were no leucocytes present in the perineurium or between nerve bundles. There were fibroblasts present about the nylon suture and occasional lymphocytes.

The extensor tendons of the forelegs of three dogs were exposed by a longitudinal incision and the tendon sheaths incised. Three tendons of the foreleg of each dog were severed transversely and immediately repaired, two of the tendons with nylon suture and one with silk in each dog. The sutures were placed through the tendon about one-half inch proximal to the severed end and tied to the tendon edge forming long tension sutures which were then tied to each other across the gap. Two



Fig. 5.—Photomicrographs of an end-to-end anastomosis of extensor tendon twenty-eight days. No. 000 nylon suture appears in the tendon without evidence of infiltration of white cells. ( $\times 45$ .)

interrupted sutures were placed through the severed ends to approximate the cut surfaces. The superficial fascia and skin were closed with nylon. The forelegs were then encased in plaster of Paris casts from humerus to phalanges and allowed to remain for two, three, and four weeks, when segments of the tendons were removed and the dogs used for other suture experiments.

Examination of the tendons after two weeks revealed practically the same findings in all tendons whether silk or nylon was used. There was a thickening of the suture line at the end of two weeks which diminished in bulk at the third week; and at the end of four weeks there was practically no thickening so that it was difficult to find the suture material except for the marker. The microscopic examination of the nylon is demonstrated in Fig. 5. There were no round cells or

amount. Edema of the edges was still marked. The nylon suture had cut through in two places. The right wound was pink and slight edema was present. The nylon suture was absent from two sutured areas. After twenty-one days the wound on the left was free of pus, but a serous discharge persisted from the suture holes. There were no gaps in the wound, but serum caused an elevation of the skin. The right wound was well healed. The dogs were sacrificed at twenty-four days and the skin opened through the original incisions. The right fascia held securely in the silk and nylon ties; however, the fascia retracted between the sutures. Grossly the silk and nylon appeared the same. The left fascia and muscle were covered by a mucoid material and the sutures were lying securely knotted in the fascia, the edges of which were retracting. Microscopic examination of the left and right fascia and muscle presented a marked infiltration with leucocytes about the silk



Fig. 4.—Photomicrograph of section of bladder in which No. 000 nylon was used to close the cystotomy. There is evidence of presence of round cells about the suture. ( $\times 50$ .)

and in between its fibers. There was marked separation of the fibers with a fragmentation of the silk. The nylon was surrounded by cuffs of leucocytes and lymphocytes which are not as closely packed together as about the silk suture. At this period, of twenty-four days, the infection seemed to be in a less acute stage about the nylon with a shift to lymphocytes, while leucocytes still surrounded the silk.

*Use of Nylon in Perineurium.*—The sciatic nerves of three dogs were exposed and only partially severed to prevent a complete paralysis which is usually followed by infection in the wound. The perineurium was sutured with No. 000 nylon which brought the nerve ends together. No attempt was made to cover the sutured areas with fat, but the nerve was

## HOW LONG SHOULD OPERATION BE DEFERRED IN CASES OF INTENSE JAUNDICE OF RECENT ONSET?

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WHILE the majority of cases of intense jaundice are due to hepatitis,\* stone in the common duct, or cancer implicating the bile passages, the differential diagnosis of these three conditions is often extraordinarily difficult. Stone and cancer are, of course, unusual in young people; previous attacks of colic point to stone and the demonstration of a huge distended gall bladder or metastatic nodules practically clinches the diagnosis of neoplasm, but all signs can fail, including the various laboratory tests, and one may observe the patient day after day without reaching a definite conclusion. This group of undiagnosable cases of intense acute jaundice is a sore trial to the physician, particularly with reference to surgical interference. If the patient has stone in the common duct, operation is, of course, in order, and if an attempt is to be made to do anything about cancer, then the sooner the better. But if the jaundice is due to hepatitis, one is dealing with a nonsurgical condition and exploration not only serves no purpose but may harm the patient. In a recent case, for example, an elderly man, intense jaundice with acholic stools had existed for three weeks without definite diagnosis being possible. He was in splendid condition and seemed to tolerate his icterus unusually well. At operation there was found not the suspected stone but hepatitis with colorless material in the ducts and in the gall bladder, which was drained. In spite of thorough preparation with glucose and saline solution, bile salts, and vitamin K, the patient lapsed into coma with high blood urea and fever and died within three days.

It has been our impression that surgeons faced with this problem of intense jaundice of uncertain cause have no very definite basis for deciding just when interference is in order, if at all. What happens as a rule is that after a variable and irrational period of observation those in attendance feel they have waited "long enough" and that they had better "look in." They have not clearly formulated the problem in some such way as this: It is desirable to operate for stone or cancer, but undesirable to operate because of hepatitis. Since hepatitis usually clears up spontaneously, how long should one wait for such clearing in a doubtful case of intense jaundice before concluding that one is not dealing with hepatitis and that operation is therefore in order?

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\*In this paper hepatitis is used to include what is commonly spoken of as catarrhal or acute infectious jaundice.

leucocytes but a few plasma cells and fibroblasts surrounding the suture material. The microscopic sections of the tendon with silk revealed the presence of three rows of lymphocytes and leucocytes surrounding the silk, a definite irritation as compared with nylon.

#### SUMMARY AND CONCLUSIONS

Experiments performed with nylon suture in fascia and muscle reveal the use of monolithic suture to be superior to twisted nylon and silk, causing less irritation to, and being the least affected by, the tissues. Monolithic strands, however, are more difficult to handle, are not as flexible as the twisted filaments, and are thus less practical for deep suture of abdominal viscera. The knots are bulky and not easily encapsulated.

Multifilament nylon, especially No. 000, is easily handled, is flexible, and can be threaded without difficulty on fine needles. This suture approximates tissues without cutting through. The material is more elastic than silk and in the fascia and muscle does not cause as much irritation to and is not attacked by, the white blood corpuscles, as acutely as a similar-sized silk suture.

Experiments performed on stomach, jejunum, and ileum show excellent results with nylon as to its lack of irritative properties and good retentive ability, even with such small caliber material as the No. 000 gauge.

The use of nylon in attaching hollow organs to the abdominal wall as the sigmoid colon and the bladder does not result in fistulous tracts, while the viscus remains securely attached to the wound.

Bladder tears closed with No. 000 nylon hold securely and do not result in fistulous tracts.

Nylon placed in tendon and nerve is well tolerated, does not call forth a leucocytic or even lymphocytic response. The fine-sized No. 000 suture will hold the tendon securely and does not occupy much space.

Nylon in infected wounds acts much the same as silk in securely holding the tissues and remaining unchanged. Nylon allows for an early change from leucocytic to lymphocytic response about the suture, while the silk keeps the leucocytes present for longer periods.

Nylon has all the good qualities of silk and in addition is stronger, less irritating, and does not allow for as marked an invasion of its interstices as silk.

Nylon may be boiled several times without losing its original tensile strength.

#### REFERENCES

1. Davis, Loyal, and Aries, Leon J.: An Experimental Study Upon the Prevention of Adhesions About Repaired Nerves and Tendons, *SURGERY* 2: 877, 1937.
2. The DuPont Magazine 32: 1-2, 1938.

TABLE II

SUMMARY OF OBSERVATIONS OF DURATION OF JAUNDICE IN CASES OF HEPATITIS BEFORE CLEARING BEGAN

CASE NO.	AGE	SEX	DURATION OF JAUNDICE UNTIL CLEARING BEGAN* (DAYS)	HIGHEST VAN DEN BERGH (UNITS)	HIGHEST ICTERIC INDEX (UNITS)
1	8	F	6	---	---
2	48	F	6	10	53
3	30	M	7	11	54
4	12	M	7	---	---
5	26	F	7	---	83
6	34	M	9	18	66
7	43	M	10	8	50
8	35	M	10	15	---
9	58	F	14	60	200
10	44	M	14	13	68
11	40	M	16	40	129
12	38	M	17	12	---
13	38	M	18	---	33
14	34	M	18	24	65
15	45	F	21	60	166
16	67	M	21	49	144
17	67	M	21	---	160
18	25	M	21	6	34
19	31	M	21	50	166
20	50	M	21	56	256
21	49	F	21	---	50
22	50	F	23	35	144
23	35	M	23	8	62
24	48	M	26	110	300
25	38	M	30	15	75
26	37	M	30	5	33
27	53	M	35	8	50
28	68	M	35	25	100
29	22	M	35	50	208

\*The duration was determined as accurately as possible, but there are doubtless small errors in some of the cases, especially in dating onset of jaundice as noticed by patient or friends.

TABLE III

CLEARING OF JAUNDICE IN CASES OF HEPATITIS IN RELATION TO DURATION OF THE DISEASE

DURATION (WEEKS)	NO. OF CASES BEGINNING TO CLEAR	PERCENTAGE OF WHOLE
5	29	100
4	24	83
3	14	48
2	8	28
1	2	7

From Table II some other points of interest can be deduced. Hepatitis is not particularly a disease of young people as some propose. Table IV shows, for example, that two-thirds of our cases were between 31 and 50 years of age, and there were nearly as many in the sixth and seventh decades as in the first three. The fact that the patient is not young does not therefore justify the surgeon in passing over the possibility of hepatitis.

As a background with which to compare the statistics to be discussed presently, the above question was posed to five surgeons, all senior staff men of large experience, and to five internists. The surgeons gave it as their opinion that with intense obscure jaundice of recent onset one should not delay operation for over one week (one opinion), ten days (two opinions) and two to three weeks (two opinions). Walters and Snell<sup>1</sup> in their recent monograph concur in the feeling that only a brief period of watching is justifiable. The internists, on the other hand, apparently aware of rare instances of acute hepatitis that clear up entirely after several months of jaundice, all felt one should wait from four to eight weeks.

In view of all this confusion it seemed important to get the facts as to how soon the jaundice begins to lessen. A search through our files yielded twenty-nine cases, proved by their subsequent course to have simple hepatitis, in which it was possible to determine with reasonable accuracy the number of days from onset of jaundice to the beginning of subsidence. The trend of the van den Bergh test or of the icterus index measured at frequent intervals together with the presence or absence of bile in the stools were the pertinent data. Table I is a

TABLE I

DATA FOR CALCULATION OF DURATION OF JAUNDICE FROM ONSET UNTIL CLEARING  
BEGAN IN PATIENT F\*

	VAN DEN BERGH (UNITS)	ICTERIC INDEX (UNITS)	BILE IN STOOLS
July 1, 1936, jaundice first noticed			
July 16	50	208	
July 22	50	178	
July 27	45	182	0
Aug. 3	45	166	0
Aug. 8	27	150	+
Aug. 10	--	--	+++
Aug. 15	24	92	
Aug. 22	--	60	

\*Onset of resolution of jaundice is clearly not earlier than Aug. 3 nor later than Aug. 8. The total duration of the jaundice until clearing began is then not less than thirty-four days and not over thirty-nine days.

protocol of an illustrative case, and Table II gives a summary of all the observations. Table III is of special importance because it shows how soon jaundice begins to subside in various cases of hepatitis. It is seen, for example, that after two weeks only 28 per cent of the cases had begun to clear. Obviously, then, the surgeon who interferes after so short a period of observation will operate ill advisedly on many people who would later recover spontaneously. Even three weeks is too brief a time and in order to be sure that one is not dealing with a spontaneously resolvable icterus one should wait in doubtful cases for at least four and perhaps five weeks. No harm will be done, even if stone or cancer turns out to be present, by a delay of this duration, especially now that a hemorrhagic tendency can be controlled by vitamin K and bile salts.

# PAPILLARY CYSTADENOCARCINOMA OF THE PANCREAS

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A PATIENT suffering from papillary cystadenocarcinoma of the pancreas was seen recently at the Massachusetts General Hospital. Lichtenstein,<sup>28</sup> in 1934, reported a case showing this lesion, and stated that there appeared to be no previous authentic case in the American literature. He reviewed the literature up to 1934. Proved recorded instances of this rare disease are so few that it was considered desirable to report this recent case in detail. A brief review of the literature is given below and is followed by a presentation of the case.

*Incidence.*—Any sort of a cyst of the pancreas is uncommon, and malignant pancreatic cysts are rare. White<sup>48</sup> found only 3 cases of pancreatic cyst among 6,708 autopsies at Guy's Hospital in London. Young<sup>49</sup> reported in 1937 that there had been only 5 cases of pancreatic cyst recorded at the Massachusetts General Hospital during the previous seventeen years, and that 2 of those 5 had developed malignancy. No further pancreatic cysts have been recorded in that hospital since 1937. Friedenwald and Cullen<sup>10</sup> reported malignancy in 3 out of a series of 7 pancreatic cysts. However, the incidence of malignancy in these two small series must be relatively high, for Mahorner and Mattson<sup>30</sup> state that, among 88 patients with pancreatic cysts treated surgically at the Mayo Clinic, there were only 4 with carcinomatous cysts, or 4.5 per cent. Lazarus<sup>26</sup> mentions a series of 14 pancreatic cysts without a single instance of malignant degeneration.

Cases of malignant or probably malignant pancreatic cysts which have been more or less completely reported in the literature seem to be few enough to present in one small table (Table I). In a textbook of special pathologic anatomy by Kaufman<sup>23</sup> there is mentioned one case of malignant papillary cystadenoma of the pancreas in a 42-year-old woman, but no case history is presented. Several other instances of this disease have been mentioned in the literature, but they were very incompletely reported. Of the 21 cases in Table I in which sex was mentioned, 10 were males and 11 were females. Age varied from 34 to 79 years, with an average of 53 years. McWhorter<sup>32</sup> reported that cysts of the pancreas occur about equally in males and females. Oser<sup>34</sup> in a series of 121 cases of pancreatic cyst found 60 in males and 61 in females, and reported that, statistically, pancreatic cysts occurred in men most commonly in the fourth decade and in women in the third decade. In our series of malignant pancreatic cysts, as would be expected, the age group is slightly older. On the other hand, Leven<sup>27</sup>

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TABLE IV  
AGE DISTRIBUTION OF CASES OF HEPATITIS

DECADE	NO. OF CASES	PERCENTAGE
1-10	1	3.5
11-20	1	3.5
21-30	4	14.0
31-40	10	38.0
41-50	8	28.0
51-60	2	7.0
61-70	3	10.0

Table II shows also that there is no exact relation between the intensity of the jaundice and its persistence. A profound jaundice may resolve quickly; a milder icterus may persist for weeks.

#### DISCUSSION AND SUMMARY

An inquisition of experienced surgeons revealed the general feeling that exploratory laparotomy should be done in undiagnosed cases of recent intense jaundice after only a brief (one to two weeks) period of observation. The same opinion is expressed in the literature. We have pointed out that such a period is far too short to eliminate most cases of acute hepatitis, a condition in which surgery is not only useless but may be harmful. Actual statistics on the duration from onset of jaundice to beginning of resolution show that a period of observation of at least a month is necessary to rule out hepatitis with any degree of certainty. In contrast to surgeons, internists, perhaps more aware of the occasional case of hepatitis which does not resolve for two or three months, are inclined to wait too long before advising operation.

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1. Walters, Waltman, and Snell, Albert M.: Diseases of the Gallbladder and Bile Ducts, Philadelphia, 1940, W. B. Saunders Co., p. 357.

	7	Friedenwald and Cullen <sup>10</sup>	56	M	"Indigestion" 15 yr.	Drainage	Marsupialized 5 yr. after first operation and died 6 mo. later	(?) Adenocarcinoma
8	Gallagher <sup>11</sup>	79	M	Loss of weight for 10 mo.; abdominal tumor noticed 1 mo.	Drainage		Died 5 wk. later	Autopsy showed "carcinoma of the pancreas,"
9	Hartmann <sup>12</sup> (Fitz <sup>9</sup> )	53	F	3 mo. of epigastric pain	Marsupialization		Died 6 wk. later	Autopsy showed cystic epithelioma of pancreas
10	Hopkins <sup>17</sup>	76	M	Jaundice 5 wk.; loss of weight; dragging sensation in region of stomach; glycosuria first noticed 3 days before death	None		Died 5 wk. after onset of jaundice	Autopsy showed 7 cm. benign pancreatic cyst with carcinoma in its wall
11	Lichtenstein <sup>28</sup>	44	F	Upper abdominal tumor 6 yr. with ascites	None		Died	Post-mortem examination showed papillary cystadenocarcinoma of pancreas with metastases to peritoneum, omentum, and liver
12	Luecke (Senn <sup>40</sup> )	43	F	Abdominal swelling increasing for 6 mo.	Drained 27½ pints of ascitic fluid at laparotomy		Died 3 days postoperatively	Multilocular pancreatic cyst; microscopic: colloid cancer evidently with origin in pancreas and carcinomatosis
13	Mahorner and Matteson <sup>30</sup>				Laparotomy disclosed large cystic tumor with nodules on its surface and in liver; biopsy of liver nodules			Carcinoma

TABLE I  
PROBABLE MALIGNANT CYSTS OF THE PANCREAS

CASE	AUTHOR	AGE	SEX	SYMPTOMS	OPERATION	RESULT	PATHOLOGIC REPORT
1	Bachr and Klemp- erer <sup>3</sup>	50	F	Vomiting and abdominal pains 2 yr.; upper ab- dominal mass 2 yr.	None	Died 2 yr. 10 mo. after onset of ill- ness	Autopsy showed cystad- enoma of body of pan- creas with metastases
2	Boston City Hos- pital (No. 768395)	34	F	Epigastric pain; pain in back; vomiting 4 wk., loss of 20 pounds; jaundiced; urine negative	Exploratory laparot- omy; biopsy of liver	Died 12 days postop- eratively	Autopsy showed large hard pancreas, 6 cm. cyst in tail; liver me- tastases "papillary cystadenocarcinoma,"
3	Burbank Hospital (Fitchburg, Mass.) (No. 70447)	72	M	Abdominal soreness several months; jaundice 2 mo.	None	Died	Adenocarcinoma head of pancreas; papillary adenocystoma of head of pancreas, size of walnut
4	Fitz <sup>4</sup>	36	M	Pain in lower dorsal and lumbar regions 3 mo., with development of upper ab- dominal tumor	Excision	Recovery from opera- tion	(?) Malignancy
5	Friedenwald and Cullen <sup>10</sup>	50	F	Abdominal swelling, 3 yr. with occasional attacks of colic, nausea, and vomit- ing	Drainage	2 yr. postoperatively had developed jaun- dice, glycosuria, and recurrent mass	None
6	Friedenwald and Cullen <sup>10</sup>	58	F	Recently observed mass in left upper abdomen; weight loss and indiges- tion; urine, sugar—0	Marsupialized	Mass reappeared; wound ulcerated; died 6 yr. postoperatively	Biopsy of wound ulcera- tion showed "adeno- carcinoma," just be- fore death

21	(d) David	45	M	Rapidly growing tumor filling abdomen; weight loss	Aspiration 4,000 c.c. bloody fluid; abdomen closed without drainage	Died few days post-operatively	Autopsy showed "degenerating cystic tumor"; microscopic: "degenerated tissue"
22	Mixer	40	F	Painless swelling of abdomen 3 to 4 yr.; urine, sugar, "green without sediment"	Total excision	Doing well 10 mo. postoperatively	Papillary cystadenocarcinoma of pancreas
23	Prosorowsky <sup>36</sup>	78	M	No pancreatic symptoms	First stage suprapubic prostatectomy	Died postoperatively	Post-mortem examination showed pancreatic tumor containing a few small cysts and one nodule of malignant degeneration
24	Speese <sup>42</sup>	49	F	Cyst of pancreas operated on 10 yr. before (partial excision and marsupialization); urine, no sugar	Marsupialization, followed 7 yr. later by excision of tumor of abdominal wall	Well 7 yr., then developed malignant cystic adenoma which was excised	"Proliferating cystadenoma of the pancreas," (second operation)
25	Young <sup>43</sup>	34	F	Painless abdominal swelling 4 yr.; weight loss several months	Partial excision; marsupialization	Died 7 yr. later of malignancy; proved by biopsy of sinus tract before death	Multilocular cystadenoma at operation

TABLE I—CONT'D

CASE	AUTHOR	AGE	SEX	SYMPTOMS	OPERATION	RESULT	PATHOLOGIC REPORT
14	Mahorner and Mattson <sup>30</sup>				Part of cystic mass 20 by 25 cm. of pancreas was removed	Recovery from operation	Cystadenocarcinoma
15	Mahorner and Mattson <sup>30</sup>				Cystic tumor containing 4 liters of fluid removed from tail of pancreas		Carcinoma of pancreas
16	Mahorner and Mattson <sup>30</sup>				Pancreatic cyst was drained	Died following operation	Autopsy showed carcinoma of pancreas
17	Massachusetts General Hospital (No. 246951)	34	M	Epigastric pain (2 yr.); urine negative	Drainage	Recovery from operation	Cyst wall shows an occasional mitotic figure
18	McWhorter <sup>32</sup> (a) Kullke	45	F	Pancreatic cyst operated on 13 yr. before; tumor recurred 10 yr. later	Drainage	Died 2 mo. after biopsy	Biopsy of sinus 18 mo. after second operation showed malignant papillary adenoma
19	(b) Phemister	64	M	Pains in abdomen and back 6 mo.; abdominal tumor 3 mo.	2,000 c.c. clear fluid aspirated, mesenteric biopsy	Died 3 mo. postoperatively	Adenocarcinoma
20	(c) Graham	68	M	Progressive jaundice, fullness in epigastrium; weight loss 2½ mo.	Drainage of small cyst; hard mass in head of pancreas	Died day of operation	

cyst or a cyst due to compression of the ducts by a malignant growth. Macs<sup>29</sup> reported the removal of a cyst of the pancreas in which the pathologic report was cystadenoma, the chief histology being characteristic of a benign new growth, although occasional areas were observed in which an infiltration tendency was apparent.

In the ovary, papillary cystadenocarcinoma resulting from malignant proliferation of the epithelium lining a benign cyst occurs not infrequently. In the pancreas this seems to occur only rarely.

*Pathology.*—There are many different classifications of pancreatic cyst in the literature. Boyd,<sup>5</sup> in his textbook of pathology seems to have the simplest classification. He divides cysts of the pancreas into retention cysts, congenital cysts, cystadenomas, and pseudocysts. Pseudocysts are the common variety, but they are not true cysts of the pancreas and have no epithelial lining. They are usually situated in the lesser peritoneal cavity in front of the pancreas. This cyst is preceded by some injury to the pancreas, either trauma or hemorrhagic pancreatitis. As a result of upper abdominal injury, pancreatic secretions escape into the lesser peritoneal sac and, as the foramen of Winslow becomes sealed, a cyst develops. Stevenson<sup>43</sup> reported a typical case of this in a farmer whose upper abdomen was trampled on by a horse. Cushing<sup>8</sup> described another case following a blow on the abdomen. According to Boyd,<sup>5</sup> cystadenomas of the pancreas are rare tumors which may be benign or malignant. They are usually benign. McKechnie<sup>31</sup> believes that multilocular cysts are likely to be malignant.

Lichtenstein<sup>28</sup> subdivides the malignant pancreatic cysts into three classes: Essentially solid adenocarcinomas with epithelial-lined cysts; large epithelial cysts with carcinoma in the pancreas outside the cyst wall; and papillary cystadenocarcinomas.

Pancreatic cysts may originate from any part of the pancreas and may present above or below the stomach, and even below the transverse colon. Heiberg<sup>15</sup> believes that the favorite site for cystadenoma is the tail of the pancreas. Lazarus<sup>26</sup> states that the rarest position for a pancreatic cyst is in the head of the pancreas. The most common position into which the cyst grows is between the stomach and the transverse colon.

The cyst fluid may be clear, cloudy, straw-colored, greenish, brown, or bloody. Tilger<sup>44</sup> found that among 18 cases of pancreatic cysts there were 4 which showed no evidence of any pancreatic ferments present in the cyst contents. According to Judd,<sup>21</sup> one or more pancreatic enzymes are usually present in pancreatic cysts. This may be used as a distinguishing feature because, if the fluid will coagulate egg albumen or split starch, it is probably pancreatic in origin. Speese<sup>42</sup> reported a benign cyst, the contents of which showed pancreatic ferments. Seven years later (Table I), the case developed a malignant cystic adenoma in the abdominal wall, the origin of which may well

collected 566 cases of pancreatic carcinoma and found that males were twice as frequently affected as females. Pancreatic cysts are usually a disease of middle life. Among 112 cases of Müller,<sup>33</sup> 70 were between 20 and 50 years of age. Hulke<sup>20</sup> reported a case in a 47-year-old woman in whom an abdominal tumor had been noticed since girlhood (about forty years).

*Etiology.*—It seems to be agreed generally that pancreatic cysts are usually the result of some sort of obstruction to the normal secretion of the pancreatic juice in the organ. Wangensteen<sup>45</sup> states that the most frequent antecedent of a large serous cyst of the pancreas appears to be a prior attack of pancreatic necrosis. It is easy to suppose that, following pancreatitis, fibrous contraction exerts pressure on the pancreatic ducts sufficient to cause obstruction. Retention cysts are probably due to this. However, cystadenomas may be due to accumulation of fluid in cavities that are formed by spontaneous proliferation of the epithelial elements of the gland. Priesel<sup>35</sup> believes that, if there is proliferation of the cylindrical epithelium of a pancreatic duct, it may go on to form a cystadenoma or even an adenocarcinoma without infiltrating growth. He states that most authors believe that cystadenomas of the pancreas are due to aberrant pieces of pancreatic tissue which have become isolated.

Ballin and Saltzstein<sup>4</sup> cite one case of a nonmalignant pancreatic cyst which developed two months after cholecystectomy, and could find no record of any other similar case. This must be very rare. However, Judd<sup>21</sup> found gall bladder disease associated with cysts of the pancreas in 17 of his series of 41 cases. Horrocks<sup>18</sup> reported an autopsy on a case of benign pancreatic cyst associated with glycosuria and gallstones. The cyst contained about two pints of fluid, and a stone the size of a pigeon's egg was found loosely impacted in the common bile duct. Archibald and Kaufman<sup>2</sup> state that the pancreatic adenocystomas are true tumors, like the corresponding tumors of the ovary, and that they arise from the parenchymal cells by proliferation. They are, therefore, glandular structures lined with cuboidal epithelium.

Lichtenstein,<sup>28</sup> in his excellent detailed account of a case of papillary cystadenocarcinoma of the pancreas, stated that one is justified in assuming that in his patient the lesion started as a benign cystadenoma. This patient was free of any local or constitutional sign of cancer for at least five years in the presence of an upper abdominal tumor. Histologic examination of this tumor demonstrated that some of the cyst wall still showed the structure of a benign multilocular cystadenoma. Oser<sup>34</sup> believed that in the formation of cysts of the pancreas the closure of the pancreatic duct may cause stagnation and accumulation of the pathologic products, but can never be the sole cause of retention of the pancreatic juice in an otherwise normal gland. Hopkins<sup>17</sup> cites a case of pancreatic cyst which at autopsy showed what was considered to be either a carcinoma developing in the wall of a benign pancreatic

cysts of the liver and large hydrops of the gall bladder arise from the right upper quadrant, and on percussion usually can be shown to be part of the liver or continuous with it. Retroperitoneal tumor other than pancreatic cyst usually feels solid rather than fluid. Aortic aneurysm shows marked pulsation.

Diabetes mellitus was present in 3 out of 47 cases in Judd, Mattson, and Mahorner's<sup>22</sup> series of pancreatic cysts. As shown in Table I, the present case and one other are the only malignant pancreatic cysts with a definite glycosuria, although the urine was reported in only 6 of the 25 cases. Leven<sup>27</sup> states that in his series of 566 cases of pancreatic carcinoma glycosuria was an infrequent finding. Diabetes occurred in only 9 out of 134 cases of pancreatic cyst reviewed by Oser.<sup>34</sup> A case of benign pancreatic cyst which was marsupialized four years after the patient had developed diabetes and one year after the cyst was first noticed was described by Hoon.<sup>16</sup> Sodeman<sup>41</sup> reported 1 case of cystic disease of the pancreas with apparent disappearance of diabetes following operation.

Whipple<sup>47</sup> suggests giving barium simultaneously by mouth and by rectum as a diagnostic procedure. In many cases pancreatic cysts will push the stomach upward and to the right and will also push the transverse colon downward. After giving barium from above and below, x-ray will show the pancreatic cyst bulging between the stomach and the transverse colon. Fluctuation of the cyst mass sometimes can be observed on palpation. In 1903, Oser<sup>34</sup> suggested outlining the stomach in relation to a pancreatic cyst by means of the administration by mouth of tartaric acid and sodium bicarbonate, thus distending the stomach with gas. According to Wangenstein,<sup>46</sup> pancreatic cysts occasionally transmit pulsations from the abdominal aorta which lies beneath.

Typically, a diagnosis of pancreatic cyst should be considered in any middle-aged or elderly patient with a slowly enlarging, painless, cystic retroperitoneal tumor in the upper abdomen. In only 7 out of 460 cases in Müller's<sup>33</sup> series was the cyst said to be freely movable. The mass felt in cases of pancreatic cyst is dull to percussion. It may become so large that its center will slip down below the umbilicus, and thus may seem to arise from the pelvis, as in the case reported here.

*Complications.*—The complications of pancreatic cysts are hemorrhage into the cyst, perforation into the peritoneal cavity or gastrointestinal tract, and malignant degeneration. There may be jaundice from pressure on the common bile duct. Malignant cysts usually cause a slow death of the patient by extension and metastases.

*Treatment.*—If the patient will stand surgery, operation is always indicated. In the case of a benign cystadenoma many have been cured by marsupialization of the cyst. This procedure is, of course, futile in a malignant cyst, which should always be excised completely if possible. Excision may be difficult and dangerous, since the cyst often is very adherent to surrounding tissues, and also because part of the pancreas

have been in the remains of the pancreatic cyst. Lichtenstein<sup>28</sup> reported the autopsy of a patient dead of papillary cystadenocarcinoma of the pancreas and found diastase but not trypsin in the cyst contents. According to Friedenwald and Cullen,<sup>10</sup> the contents of pancreatic cysts are ordinarily alkaline, with a specific gravity of 1,010 to 1,020, and it frequently contains one or more of the pancreatic ferments.

The blood supply of pancreatic cysts is usually very generous. It is reported by Robson and Moynihan<sup>38</sup> that the splenic artery and vein may be found running either in front of or behind the tumor. The superior mesenteric vessels may cross the anterior aspect of the cyst.

*Symptoms.*—The patient may have no symptoms except for a painless swelling of the abdomen, as in the case reported below. The metabolic and digestive functions of the pancreas are usually insufficiently disturbed to attract much attention. However, ordinarily there is a long history of abdominal discomfort, sometimes resembling that of a mild cholecystitis. There may be flatulence and anorexia, and sometimes jaundice. If interstitial pancreatitis accompanies the cyst formation, there may be emaciation; large, fatty stools; muscle fibers in the stools; and sugar in the urine. This usually is not the case. Pain is due to pressure on adjoining organs. Pressure on the stomach may cause nausea and vomiting. The two cases of malignant cyst in Judd's<sup>21</sup> series suffered from loss of weight; one lost ten pounds in three months, and the other seventeen pounds in a year.

The most important symptom is a large, slowly growing, nontender, upper abdominal tumor mass. According to Oser,<sup>34</sup> in most cases one to three years elapse between the first symptoms of the disease and the time when the cyst is first observed.

*Diagnosis.*—The diagnosis of a cyst of the pancreas is not always easy, and whether or not it has undergone malignant degeneration is usually impossible to determine without biopsy. Carter and Slattery<sup>7</sup> remark that in cases of cystadenoma of the pancreas there are no diagnostic physical signs and no diagnostic laboratory procedures, the diagnosis, if made, being by the process of exclusion of other possibilities. This seems to be true for all pancreatic cysts.

Differential diagnosis of a pancreatic cyst includes ovarian cyst; pedunculated fibroid; pregnancy; hydronephrosis; mesenteric, splenic, and omental cysts; echinococcus cyst of the liver; hydrops of the gall bladder; retroperitoneal tumor; and aortic aneurysm. Ovarian cyst, pedunculated fibroid, and pregnancy can usually be ruled out by pelvic examination. Ovarian cysts are characteristically more mobile than pancreatic cysts. In ovarian cysts the hollow viscera tend to be pushed backward, and in pancreatic cysts forward. Hydronephrosis can be ruled out by pyelogram. Hneper,<sup>19</sup> however, cited a case of cystadenoma of the pancreas in which the tumor had caused a hydronephrosis, evidently by pressure on the left ureter. Mesenteric and omental cysts are usually mobile. Splenic cysts arise from the left side. Echinococcus

mortality in 28 cases totally extirpated and 55 per cent in 9 cases partially extirpated.

In Table I, 23 of the 25 cases of probable malignant pancreatic cyst were reported as to end result. The known mortality within seven years of operation was 57 per cent. Nine of the cases died within two months of the operation, and 4 more died within seven years. Four cases died unoperated upon. One case showed recurrence two years after operation. Five recovered from one or more operations and their future courses were not reported.

#### CASE REPORT

M. W., a white, single, 40-year-old housekeeper, was first seen on Jan. 23, 1939. Her chief complaint was a swelling of the lower abdomen, which had gradually increased in size over the past three or four years. Her appetite had been good. There was no history of abdominal pain. Her bowel movements had been regular without laxative. No abnormal stools had been noted. She had never been jaundiced. There had been no increased urinary frequency. Her weight had remained the same for several years. During the past six months her catamenia had been somewhat irregular and scant.

Two months previously she had had an iridectomy performed on the right eye for acute glaucoma. There had been an excellent convalescence from this operation. Two urinalyses done at that time had been reported negative. The ophthalmologist had noted that her abdomen contained a mass the size of a seven-month pregnancy and had advised her to consult an abdominal surgeon. She had had no previous operations; no history of abdominal injury could be obtained.

Physical examination showed a thin, somewhat pale 40-year-old woman in no immediate distress. The lower abdomen contained a nontender protuberant mass the size of a cantaloupe melon, extending from the pubic symphysis to about  $3\frac{1}{2}$  inches below the costal margins. The mass was firm and resistant. No fluctuation could be elicited. It was slightly movable laterally and on deep inspiration moved slightly up and down. Rectal examination showed that the abdominal mass was apparently unconnected with the cervix. The cervix seemed normal in size and position. The mass was then thought to be either an ovarian cyst or a pedunculated fibroid. Urinalysis was again negative, and she was admitted to the Baker Memorial Hospital. The urine specimen taken immediately before operation showed, for the first time, a "green without sediment" test for sugar, using Benedict's solution.

The operation was performed by Dr. Charles G. Mixer. Under ether anesthesia the abdomen was opened through a seven-inch left paramedian incision extending from the pubic symphysis to a point about one and one-half inches above the umbilicus. This made possible the palpation of a large cystic mass which arose from the region of the pancreas. The transverse colon lay flattened over the inferoanterior aspect of this mass, and the transverse mesocolon was pushed down by the inferoposterior aspect of the mass. The gastrocolic omentum lay over the anterior aspect of the tumor with the stomach lying above it. The duodenum lay to the right of the base of the tumor. The tumor itself (Fig. 1) was the size of a large cantaloupe with cystic nodulations and very large veins lying on its surface. An opening was made through the arcade of the transverse mesocolon, carried down to the wall of the tumor, and, although the tumor was adherent to surrounding structures, a fairly good line of cleavage was obtained. Another incision was made through the gastrocolic omentum and a similar line of cleavage was developed. Considerable bleeding was encountered from the unavoidable tearing of small blood vessels, but the entire

itself may have to be removed. In Judd's<sup>21</sup> series of 41 cases of pancreatic cyst, the entire cyst was removed in only 5 cases. He believed that, if too much of the pancreas was removed, diabetes might ensue.

Bozeman<sup>6</sup> is usually considered the first surgeon to have successfully removed a pancreatic cyst. In 1882 he published an account of removing a cyst of the pancreas weighing 20½ pounds. This operation was performed "under Listerism." The cyst was reported to have had a pedicle only three-quarters inch in diameter.

When complete extirpation is impossible, marsupialization, first advocated by Gussenbauer<sup>14</sup> in 1883, has become the accepted form of treatment of benign pancreatic cysts. This treatment, of course, functions best with unilocular cysts. Richardson,<sup>37</sup> in 1895, marsupialized a benign pancreatic cyst successfully. Marsupialization is done best by suturing the wall of the cyst to the parietal peritoneum. This produces a fistula, which may drain for months or even years. A case which was still draining from the fistula after fourteen years was observed by Kerr.<sup>24</sup> Wangenstein<sup>45</sup> feels that cystadenomas of the pancreas should always be excised if possible, for he believes that marsupialization fails to cure them and that they may be the progenitors of carcinoma.

Gordin<sup>13</sup> reported a benign pancreatic cyst which he was unable to remove, but which he packed with gauze saturated with sodium morrhuate. He felt that the sclerosing action of the drug was helpful in producing a successful result. Half-strength tincture of iodine and also 25 per cent glucose were used for the same purpose by Angel.<sup>1</sup>

According to Lahey and MacKinnon,<sup>25</sup> postoperative x-ray therapy is distinctly worthwhile in cases of carcinoma of the pancreas. Nothing was found in the literature concerning x-ray therapy of papillary cystadenocarcinoma of the pancreas.

*Mortality.*—In Judd's<sup>21</sup> series of 41 cases there were no immediate deaths from operation. The treatment was as follows: Drainage of the cyst cavity alone in 31 cases; enucleation of the lining membrane in 3 cases; removal of the entire cyst in 5 cases; and no operation on the cyst in 2 cases. However, in this same series one patient died a little over a month after operation and necropsy showed carcinoma of the liver and pancreas. In one other case "carcinoma was found at the time of operation," and the patient survived several months. Two other patients died within two months of operation, one of acute nephritis, and another of acute hemorrhages, pancreatitis, and acute yellow atrophy of the liver. Schmieden and Sebening<sup>29</sup> collected 128 cases of pancreatic cyst which had been operated upon and found a mortality of 15 patients. Lazarus<sup>26</sup> states that of 131 cases marsupialized by Gussenbauer's technique only 7 cases died, and of 24 cases of extirpation 6 died.

Godel<sup>12</sup> in 227 collected cases of pancreatic cyst found a mortality of only 3 per cent in 190 cases marsupialized, as against a 10 per cent

mass was enucleated and was found to arise from the body of the pancreas in about the midline, approximately one and one-half inches from the head. The tumor was sessile and had not even a short pedicle. Enucleation of the cyst left a defect about the size of a 50-cent piece involving the midportion and inferior margin of the pancreas, but leaving its superior margin intact. The defect was sutured together with interrupted plain catgut. The rents in the gastrocolic omentum and the transverse mesocolon were then closed with continuous chromic catgut. The circulation of the transverse colon was not impaired. The appendix was then removed and the wound closed in layers, without drainage. A transfusion of 500 c.c. of citrated blood was given following the operation.

Convalescence was excellent. Her temperature never rose over 100° F., and she was allowed up in a chair on the fourteenth day after operation. Postoperative urinalyses and blood sugars showed a mild diabetes, not sufficiently severe to require insulin.

The pathologic report was "papillary cystadenocarcinoma of the pancreas." The tumor (Fig. 1) was described as "a tense, fluctuant, thin-walled, smooth surfaced, purple-red and gray, slightly lobulated cyst measuring roughly 15 cm. in diameter, and weighing 2,050 Gm. On section, dirty brown, thick fluid containing fat droplets is extruded. The cyst wall is lined with a number of nodular green-brown soft masses which project from the surrounding pink wall into the cavity of the cyst. The largest cavity measures 12 cm. in diameter and there are four or five other cavities smaller but similar to the one described. Microscopic examination of the solid masses (Fig. 2) showed a well-differentiated adenocarcinoma."

X-rays of chest, spine, and pelvis showed no evidence of metastatic malignancy. A postoperative gastrointestinal series showed no evidence of obstruction or extrinsic masses.

The patient was discharged home on the seventeenth postoperative day with instructions as to a moderate diabetic diet. She was seen again five weeks after operation and was gaining strength and weight very well. The wound was solidly healed. At last visit, ten months following operation, she had gained eight pounds and showed no evidence of recurrent malignant disease. She was still dieting without insulin for a mild diabetes.

#### SUMMARY

1. Papillary cystadenocarcinoma of the pancreas is a rare disease of which very few cases have been reported in detail in the literature.

2. The relative incidence of malignant to benign pancreatic cysts varies in different reports, but it is probably about 9 per cent.

3. In its early stages the symptoms of a malignant pancreatic cyst are the same as those of a benign one.

4. The chief early symptom of a benign or malignant pancreatic cyst is a slowly growing upper abdominal tumor, with or without digestive disturbances.

5. The only adequate treatment of a malignant pancreatic cyst is complete excision.

6. A detailed case report is presented of the successful complete extirpation of a papillary cystadenocarcinoma of the pancreas.

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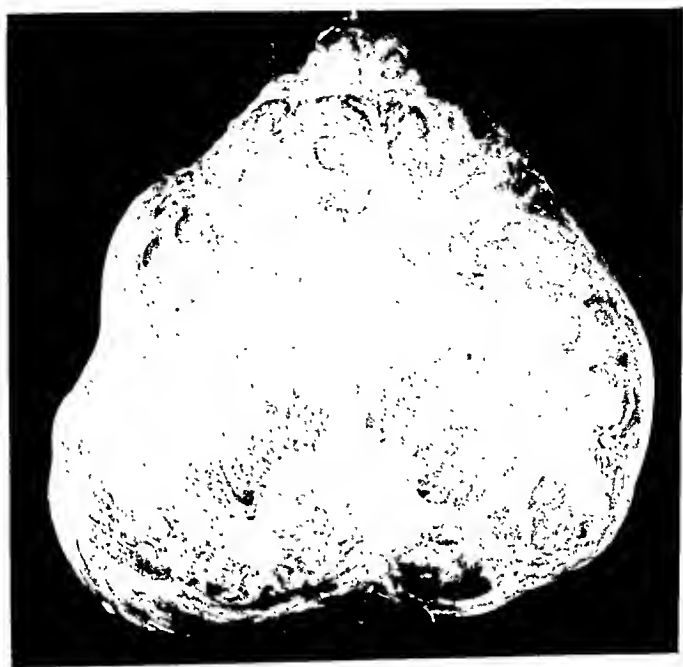


Fig. 1.—Papillary cystadenocarcinoma of the pancreas weighing 2,050 Gm. Note absence of papillary processes on the surface.



Fig. 2.—Photomicrograph showing well-differentiated adenocarcinoma.

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Ashby<sup>1</sup> in which three children developed a left-sided alopecia two weeks after they were struck by lightning. They had a return of their hair in approximately six months.

Among the organs of special sense that have been affected by lightning stroke are the ears and eyes. Silverman<sup>29</sup> reported a case of unilateral deafness. The ear bled for three days after the accident, but the author did not state whether or not spinal fluid also came from the ear. Examination of the ear, when the bleeding had stopped, showed reddening of the tympanic membrane but no lacerations of the drum or canal. Slingerland<sup>30</sup> reported a case of conjunctivitis and internal strabismus which recovered without sequelae. Lea's<sup>23</sup> case of conjunctivitis and paresis of the ciliary muscles improved somewhat, but the eyes had remained weak and irritable up to the time the case was reported. Cataracts have been noted with some degree of frequency following lightning stroke.<sup>4, 10, 17, 24, 27, 32</sup> Several authors have reported good results following operation for this type of traumatic cataract.

Lesions of the nervous system following lightning stroke have been very bizarre and varied.<sup>5, 8, 25, 26</sup> Muscular weakness and paresthesias have been the most common findings. Complete paralysis, either permanent or temporary, has been recorded and in each case the question of hysteria has arisen. The return of function has been so rapid in some cases that the exact location and type of the pathologic lesion may be under dispute. Critchley<sup>6</sup> described seven pathologic findings in people injured by lightning or electricity: (1) local petechial hemorrhages throughout the brain; (2) softening and edema of the brain; (3) ballooning of the myelin sheaths of the peripheral nerves and changes in the nerve fibers themselves; (4) fragmentation and tortuosity of the axones, breaking down of the sheaths of Schwann and fusion of their nuclei; (5) a change to a spiral-like appearance of the muscles; (6) dilation of the perivascular spaces in the brain stem and cord, probably due to the electrolysis; and (7) chromatolysis of the nerve cells of the cord and brain. These varied pathologic processes explain many of the unusual clinical pictures found in the literature. In some cases, however, it is difficult to correlate the localized areas apparently involved and the reported signs and symptoms.

The authors have been able to find reports in the literature of five skull fractures caused by lightning stroke and one case in which a sequestrum was spontaneously extruded three months after the injury. Death had occurred practically instantaneously in all cases, except the one with the sequestrum, and in several there were large burns or lacerations associated with the cerebral injury. Schottin<sup>25</sup> described the first case in 1831. This patient was in profound shock when first seen and he died soon after this. There was present a large stellate fracture of the right parietal bone immediately underlying a laceration of the scalp.

# THE SURGICAL ASPECTS OF LIGHTNING STROKE

## WITH A CASE REPORT

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PEOPLE struck by lightning have presented many unique pathologic changes. Burns, fractures, lacerations, cataracts, and lesions of the nervous system have all been reported. If a person survives the initial shock, the prognosis, as far as life is concerned, is good. However, many cases have been reported where serious sequelae followed apparent recoveries from the initial injuries.

During the years 1924 to 1933 there were 3,849 deaths due to lightning reported within the Death Registration Area of the United States.<sup>32</sup> The mountain and southern states had the highest death rates, over 8 per one million deaths. The northeast and middle Atlantic states had the lowest rate, with 1.3 per one million deaths. Since 1934 there has been a relative increase over the average of 385 for the previous ten years, as follows: 1934, 442 deaths; 1935, 362 deaths; 1936, 409 deaths; 1937, 460 deaths.

Burns are the most common lesions due to lightning stroke and may be of any degree of severity. Reports of bizarre patterns have been recorded, such as arborescent markings, long narrow lines, localized surface burns, and burns made in shapes determined by metal objects in the clothing or pockets.<sup>5, 21, 30</sup> Associated with the burns, large lacerations may be caused by the explosive force of the lightning stroke. Wehe<sup>33</sup> reported a case in which the soft tissues were torn from the right shoulder area, thereby exposing the upper end of the humerus, the clavicle, and the muscles of that area. Hegner<sup>15</sup> reported compound fractures of the bones of the foot associated with considerable destruction of the soft parts. Perhaps the most common burn is the linear type, which marks the path of the electricity between two points on the body's surface. That part of the body which is in contact with a metal object at the time of injury usually suffers the greatest degree of trauma. In Benjamin's<sup>3</sup> case the patient was driving a truck and a large burn on his thigh was apparently the point of contact with the car. Elwell<sup>12</sup> reported the case of a boy who received a large burn and laceration of the arm in which he was carrying a metal bucket. Dunscombe-Haniball<sup>9</sup> reported a patient who received a large burn over the right side of the body and right shoulder where he was carrying a pitchfork.

Frequently the hair of the head or eyebrows is singed without associated deep burns of the skin. The most unusual report is that of



Fig. 1.—Photograph of dress which the patient was wearing at the time of the accident. Her corset and underclothes were also torn and burned.



Fig. 2.—Photograph of right side of face, showing laceration and injured ear, one week after the accident.

Post-mortem examination of the brain did not reveal any gross pathologic changes. Heffernan<sup>14</sup> reported a second case of skull fracture in 1877. Post-mortem examination revealed a diamond-shaped fracture of the right orbital plate and a layer of semifluid blood overlying the right hemisphere of the brain. No pathologic change was noted in the brain substance. Knaggs<sup>21, 22</sup> described a bilateral vault fracture which extended into the base. The cerebrospinal fluid was under increased pressure at the time of the post-mortem examination. The brain surface was injected and the vessels of the meninges were engorged with fluid blood. This was most marked in the arachnoid near the fracture. The brain substance was abnormally soft but not lacerated or necrotic.

Dunseombe-Hanibal<sup>9</sup> reported two fatal cases of skull fractures caused by lightning. Post-mortem examination in one showed a compound depressed fracture of the skull with a normal-appearing brain. In the other there were multiple simple fractures with some softening of the brain. Herrman<sup>16</sup> reported a case in which a sequestrum of the skull, 3 cm. in diameter, was spontaneously extruded three months after an injury by lightning. A large ulcer of the scalp had been present over the sequestrum and there had been accompanying signs of cerebral injury on that side.

We are reporting this case because of the somewhat unusual type of trauma and because of the recovery from lesions which formerly had resulted in death.

#### CASE REPORT

*History of the Accident.*—Inasmuch as the patient still has a complete amnesia for the details of the accident, we must depend upon circumstantial evidence and the history obtained from her husband. It is known that the patient was standing against the metal sink in her kitchen, washing the lower plate of her false teeth, when the house was struck by a large bolt of lightning. This had apparently come in along the electric light wires and grounded through the sink. The patient was found by her husband a few minutes after the accident lying upon the floor unconscious. A large piece of plaster, 2 by 2 feet in size, had been knocked out of the wall and the metal medicine cabinet which had been on the wall above the sink was found lying on the floor. The electric light meter which had been on an inside wall was found torn from its fastenings and one connecting wall plug was likewise damaged. The patient arrived at the Henry Ford Hospital at 3:40 P.M. Sept. 9, 1939, approximately one and one-half hours after the accident. She was still unconscious and could not be aroused.

*Examination.*—The most striking thing, when the patient was first observed, was her general appearance. She appeared to be in deep shock, and still her blood pressure was 120/80 and her pulse 72. She had no respiratory embarrassment and the rate was 20 per minute. Her clothes were torn and burned, especially in the front and on the right side, as shown in Fig. 1. She had a number of leather-covered metal hair curlers scattered throughout her hair and no burns were present under these. The hair over the right parietal and mastoid areas was singed, as were the eyebrows and eyelashes. The right ear was almost completely torn off and the upper one-third missing. There was a large irregularly charred and macerated laceration of the skin in the right mastoid region which measured 4 by 2 cm. The mastoid bone also appeared to have blown open, its edges being jagged and charred. Sanguineous spinal fluid dripped briskly from the canal of the right ear.

sion while the laceration of the right mastoid area was being débrided and sutured. Very gradually she regained consciousness and about six hours after the accident she could answer very simple questions, but she remained stuporous and quiet. The burns were tanned by the usual method with resorcitannol jelly and healed rapidly. Sulfanilamide was started on the day after admission as a prophylactic measure against meningitis, which we felt would be a fatal complication. In the first twenty-four hours she developed edema of the right eyelid which slowly disappeared during the succeeding three days. The external strabismus disappeared by the second day. The patient's temperature remained around 100° F. by rectum for four days and suddenly rose to 104° F. At that time she became more stuporous and had questionable neck rigidity. Lumbar punctures were done daily for six days. Cultures of the spinal fluid were negative. The cell count was 2,600 W.B.C. with 29 per cent polymorphonuclear cells and 71 per cent lymphocytes in the first specimen of spinal fluid. Chemical analysis of the spinal fluid showed the protein to be 260 mg. per cent and the sugar to be 122 mg. per cent. Sulfanilamide therapy was continued and hypertonic glucose was given intravenously periodically. She was placed in an oxygen tent and five small transfusions were given over a period of eleven days. After spinal drainage was started, she gradually improved. Lumbar punctures were done for six days. Fortunately there was no involvement of the heart or lungs. Early in her recovery she spoke with a high-pitched monotone and cerebration was very slow. As she improved and her temperature became normal she gradually regained her normal voice and intelligence. When she first was allowed out of bed and began to sit up in her room, she had an unexplained temperature of 102.8°, but it subsequently went to normal and remained so.

The burns healed as rapidly as those of a similar size and degree that are acquired in other ways. The laceration behind the right ear, which had been carefully débrided upon admission, healed without infection and the remaining portion of the ear attached itself in spite of the meager blood supply. Spinal fluid stopped draining from the ear on the seventh day after the accident.

At the time of discharge, thirty-four days after the injury, she was able to go up and about her room. Her vision was good and her husband noted no changes in her personality which could be attributed to the accident. Hearing in her left ear was fair, but poor in the right with almost complete nerve deafness. The right eardrum appeared markedly scarred in the posterior quadrant.

*Discussion.*—Although, at the time of débridement, it had not been possible to approximate the skin edges of the mastoid wound, it did heal normally. This experience substantiates that of Gem<sup>13</sup> and Slingerland,<sup>30</sup> who reported normal healing of wounds. Hegner,<sup>15</sup> Elwell,<sup>12</sup> and Dunsecombe-Haniball<sup>9</sup> stated that burns due to lightning heal slowly and Critchley<sup>7</sup> warned against hemorrhage and necrosis. The skull fracture, although not verified by x-rays, was proved clinically by the cerebrospinal otorrhea which lasted a week.

As stated above, we cannot be certain how much trauma resulted from the lightning and how much might have resulted from the fall to the floor. Because of the charred blown-open appearance of the mastoid wound and the blown-off appearance of the ear, it seemed that this part of her body had definitely been the contact point for either the entrance or exit of the lightning.

The pupils were equal and regular, but the right eye deviated outward and upward. The entire right side of her face and neck was covered by a first degree burn, and there was a second degree burn over most of the anterior chest wall. Both wrists had small second degree burns and were lacerated. The skin over the pubis had several small lacerations and a second degree burn was present. The pubic hair was singed. (Figs. 2, 3, and 4.) Examination of the chest and abdomen was negative



Fig. 3.—Photograph of chest and wrists, showing burns one week after accident.



Fig. 4.—Photograph of pubis, showing burn and loss of hair, one week after accident.

except for the above-mentioned burns and lacerations. The deep tendon reflexes were all present and equal on the two sides but somewhat diminished. No pathologic toe signs or clonus were present.

*Course in the Hospital.*—The evidence of shock promptly disappeared. Approximately one and one-half hours after the accident she began to move her extremities voluntarily, although she did not respond to commands. She vomited on one occa-

## PLEURAL EFFUSION ASSOCIATED WITH OVARIAN FIBROMA (MEIGS' SYNDROME)

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THE more common causes of massive pleural effusion are well known and easily diagnosed. Tuberculosis, pneumonia, cardiac failure, malignancy of the lung, and metastatic malignancy explain the great majority of cases of hydrothorax. That fluid in the chest may occasionally be due to a benign pelvic tumor until recently has remained unrecognized. In 1937 Meigs and Cass<sup>1</sup> reported seven cases of pleural effusion and ascites associated with a benign ovarian tumor (fibroma), in which the pleural effusion was cured by the operative removal of the ovarian fibroma. Rhoads and Terrell<sup>2</sup> also reported a similar case, and in a later report by Meigs<sup>3</sup> in 1939 he had collected fifteen cases, all showing similar characteristics of pleural effusion and ascites apparently due to a benign ovarian tumor. Although no satisfactory explanation of why pleural effusion should occur in a patient with a benign ovarian fibroma has been offered, it, nevertheless, is now well established that it can and does occur. It is of the utmost importance that internists and surgeons alike be made cognizant of these facts; for otherwise the occasional patient exhibiting this syndrome may be doomed as hopeless and inoperable.

The following case report, which will represent the sixteenth reported case in the literature, illustrates the importance of knowledge of this syndrome.

### CASE REPORT

Mrs. S. S., aged 67 years, white, American, and a widow, was admitted to the Mount Zion Hospital on July 27, 1939, complaining of: (1) shortness of breath, (2) fatigue, (3) pain in the right chest, and (4) difficulty in lying on the right side.

The family history was negative for tuberculosis and malignancy. The patient has two children living and well, aged 39 and 42 years.

*Past History.*—During the past thirty years, she had enjoyed unusually good health and had been attended for various minor ailments at intervals by her physician who had kept an accurate medical record on this patient during this period of years. Of interest in relation to her present condition are his notes showing that the patient had had an uneventful menopause in 1926. In 1933 she had a vaginal plastic operation for repair of a cystocele, and the surgeon's pelvic examination at that time showed no evidence of a tumor in the pelvis.

In April, 1935, during routine general physical examination, her physician noted a small mass in the left fornix, apparently attached to an atrophic uterus. By August, 1935, this mass had increased in size, and felt like a growing uterine fibroid. X-ray treatments were given at that time to this tumor, although no symptoms

## SUMMARY

We have described what seems to be the first case which recovered from a skull fracture with brain injury resulting from a lightning stroke. A prolonged cerebrospinal otorrhea ceased spontaneously, uncomplicated by meningitis, possibly due to the prophylactic use of sulfanilamide.

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The patient returned to San Francisco in March, 1939, under the care of her own physician, who reviewed the findings of the Los Angeles internist, and further noted that the pelvic tumor had increased considerably in size and that there was present a small amount of fluid in the abdomen. At this time, there was noted a marked increase in the amount of the pleural effusion, as demonstrated by a chest film (Fig. 1). The patient was now practically bedridden because of her dyspnea and increasing weakness, but it was thought advisable to give her an intensive course of deep x-ray therapy to the pelvic tumor. This was done during the early part of July, 1939, with no improvement in the patient's condition, although it was thought that the pelvic tumor had decreased slightly in size.

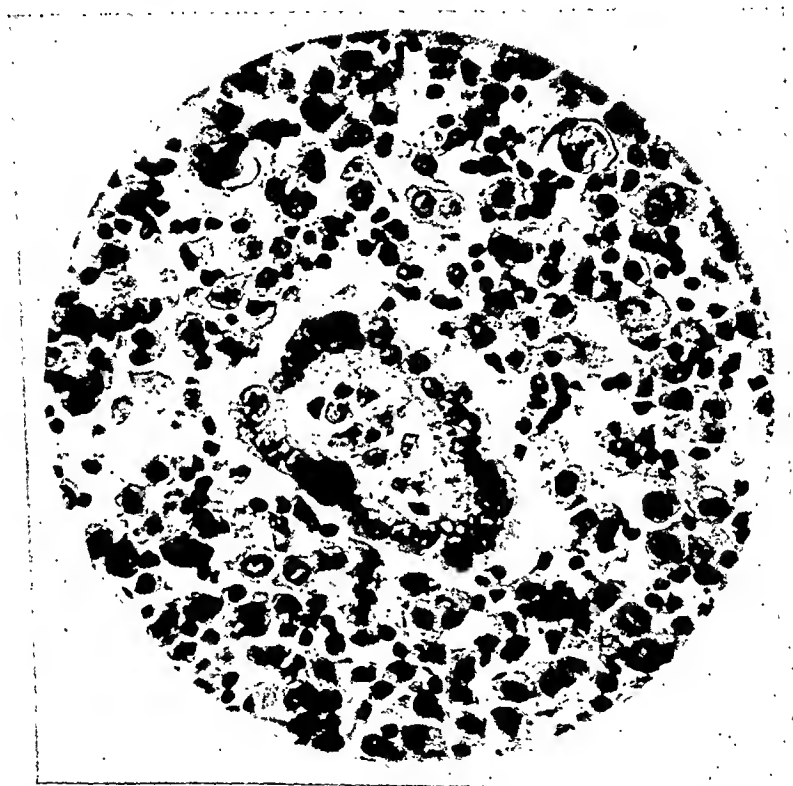


Fig. 2.—Photomicrograph of centrifuged pleural fluid. Cellular sediment is composed of mononuclear mesothelial cells, lymphocytes, and polymorphonuclear cells with the acinar arrangement of the low columnar cells in the center of the field. ( $\times 400$ .)

On admission to Mount Zion Hospital on July 27, 1939, the pelvic examination showed a hard, slightly movable tumor lying between the rectum and the bladder and occupying the entire pelvis. It could be palpated abdominally just below the umbilicus. The tumor seemed separate from the small, atrophic uterus, which appeared to be compressed by the overlying tumor mass. Fluoroscopy of the chest showed fluid in the right chest, extending to the axilla, with displacement of the heart to the left.

At consultation at this time between the patient's physician and the senior author (F. I. H.), it was suggested that there might be a relationship between the pelvic tumor and the pleural effusion, that this patient might represent a case of Meigs' syndrome. The decision was made to aspirate the fluid from the chest and to study

were being produced by it. Re-examination of the pelvis in July, 1937, still showed the presence of a small tumor in the left fornix, but as the patient was in good health no further treatment was suggested.

In March, 1938, vaginal examination showed the tumor to have increased considerably in size. It was firm and occupied almost the entire pelvis. The tumor was freely movable and strongly suggested a growing, pedunculated uterine fibroid. The patient was in excellent health. There had been no vaginal bleeding and no other symptoms referable to the tumor so no treatment was advised, and the patient was not seen again by her physician until September, 1938. At this time she complained of pains across the shoulder and some slight dyspnea on exertion, which was attributed to a beginning failure of her myocardium.

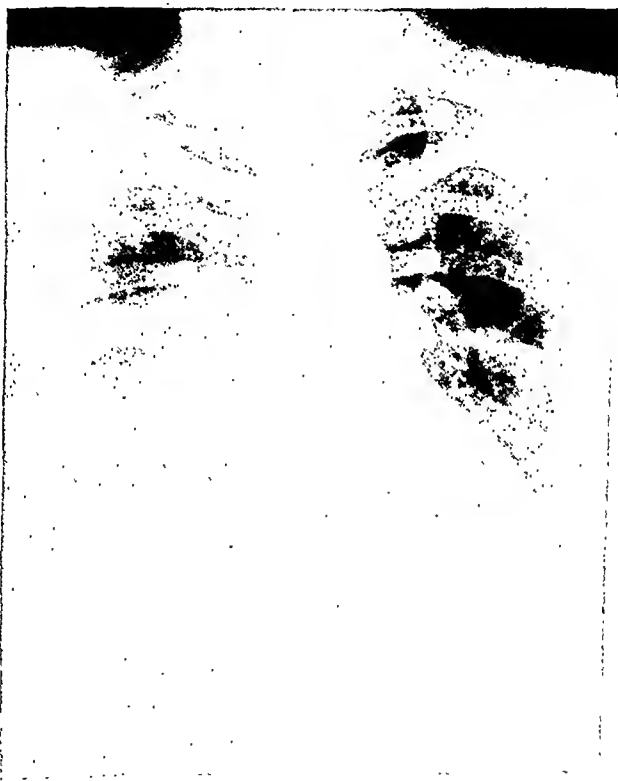


Fig. 1.—Massive pleural effusion in right side of chest.

During the next few months, she began to show evidence of increasing weakness, easy fatigue, dyspnea, and loss of weight. She visited her daughter in Los Angeles, who referred her to an excellent internist of that city for a complete check-up examination. Gastrointestinal x-rays, chest films, and electrocardiograms, as well as other studies, were made at this time. The presence of a small amount of fluid in the right chest was noted. This fluid was aspirated and studies, including guinea pig inoculation, were reported as essentially negative. The examining physician concluded that the fluid in the chest, inasmuch as it was unilateral and no other signs of congestive heart failure were present, did not represent a failing myocardium, but most probably represented a pleural effusion as the result of a malignancy of the lung.

straw-colored, ascitic fluid. In the region of the left ovary there was a large, irregular, nodular mass, which was firm to palpation, of a whitish color with reddish streaks throughout its surface. The uterus was small and atrophic, and on its anterior surface there were two very small, seedlike, subserosal, whitish areas. The right ovary was small and atrophic. The mass described on the left side was slightly adherent to the parietal peritoneum posteriorly. It was easily freed up and removed, together with the uterus and right ovary. The liver was palpated and visualized and appeared essentially normal. Complete intra-abdominal exploration was negative for any evidence of metastatic nodules or enlarged lymph glands. The exploration was considered essentially negative in all respects, except for the tumor described. The postoperative course of this patient was essentially uneventful. Her recovery was rapid and complete. At the present time, six months after her operation, she has gained weight and strength, and repeated fluoroscopic examinations of her chest have shown no evidence of a return of the pleural effusion. She states that she is enjoying the best health she has had in the last few years.

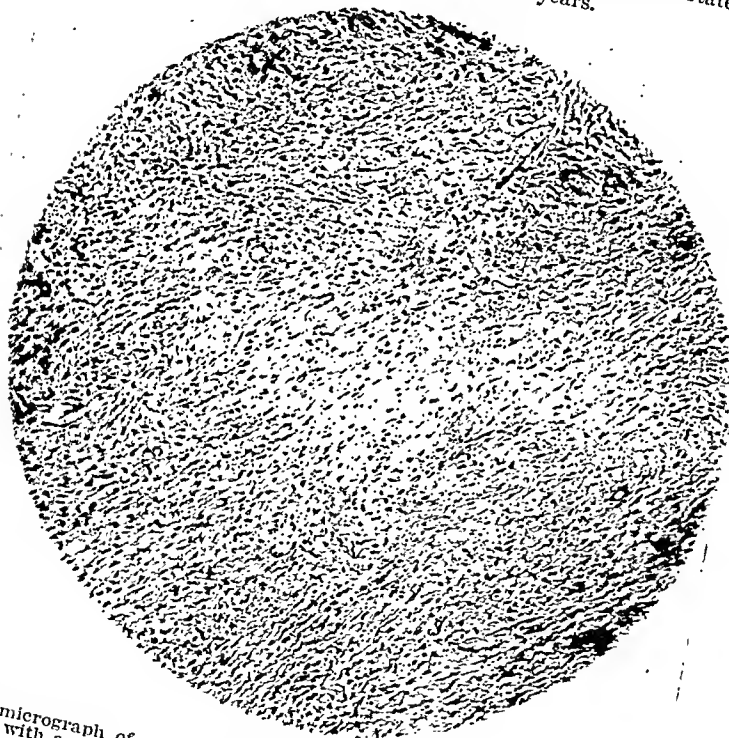


Fig. 4.—Photomicrograph of ovarian fibroma. The collagenous fibrils are loosely arranged with a slight tendency toward a fascicular formation. ( $\times 100$ .)

*Pathologic Examination* (by Dr. G. Y. Rusk).—"The specimen consists of a uterus, both tubes, the right ovary and a large, lobulated mass in place of the left ovary (Fig. 3). This large, irregularly lobulated, firm gray mass measures 13 by 10 by 6 cm. in its three dimensions. It has entirely replaced the left ovary and at the point of attachment of the tube no ovarian tissue is recognizable. The lobulations vary from 3 to 9 cm. in size, and there is a thin, smooth capsule covering them. On hemisection there are several large cysts measuring up to 4 cm. in diameter situated in the center of some of the larger lobulations. The cysts are lined by a

it microscopically. If no evidence of malignancy of the lung could be found in the centrifuged fluid, the patient was to be subjected to a laparotomy on the tentative diagnosis of ovarian fibroma producing the pleural effusion.

Thoracentesis was performed on July 27, 1939, and 3,000 c.c. of fluid aspirated from the right chest. This fluid on examination showed a yellowish, turbid color; specific gravity, 1.018; Rivolta test, slightly positive; red blood count, 360; white blood count, 740; with a differential count of lymphocytes, 77 per cent; large endothelial cells, 12 per cent; polymorphonuclear leucocytes, 9 per cent; monocytes, 2 per cent. The Gram stains showed no organisms. Guinea pig inoculations were done and were later reported to be negative. The fluid was centrifuged and the sediment dehydrated and embedded in paraffin.

G. Y. Rusk, pathologist at Mount Zion Hospital, reported that microscopic examination of this sediment revealed it to be composed of a mixture of large mononuclear cells, lymphocytes, and a few polymorphonuclear leucocytes. The large cells had a distinct oval or round vesicular nucleus that contained a small nucleolus and a fine network of chromatin strands. There were no mitotic figures. There was one nest of cells which differed from the above in that it contained low columnar cells in a distinct acinar arrangement with the nuclei arranged in a row in the midportion of the cells. There were no mitoses in these cells.



FIG. 3.—Photograph of cut section of ovarian fibroma (left) with the attached atrophic uterus and right ovary.

*Pathologic Diagnosis.*—Sediment of pleural fluid composed of mesothelial cells, lymphocytes, and polymorphonuclear cells with one acinar formation of low columnar cells (Fig. 2).

*Operation.*—On Aug. 1, 1939, under subarachnoid anesthesia, a midline incision was made, and the peritoneal cavity opened. There was noted about 200 c.c. of clear,

That these cases may be wrongly diagnosed as growing uterine fibroids is emphasized by our experience with this patient. A point of differentiation which may be helpful in other future cases is the fact that seldom, if ever, have we seen or heard of uterine fibroids developing and growing after the menopause. As ovarian fibromas on pelvic examination feel to the examining hand exactly like uterine fibroids, the preceding statement may be of considerable help in differential diagnosis.

#### SUMMARY AND CONCLUSIONS

A case is reported of a woman 67 years of age, who had been known to have a growing pelvic tumor diagnosed as a uterine fibroid for four years. She developed massive pleural effusion in her right chest, which was thought to be due to a malignancy. Abdominal operation and removal of a large benign ovarian fibroma resulted in a complete restoration to health, with no recurrence of the pleural fluid.

Based on the experience in this sixteenth reported case of Meigs' syndrome, it is our opinion that an ovarian fibroma producing pleural effusion does not respond to radiation therapy and is best treated by surgical extirpation.

Differentiation must be made between uterine fibroids, metastatic malignancy, and ovarian fibromas in the diagnosis of this condition. A correct differential diagnosis may mean restoration to health of a patient who is doomed as hopeless.

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grayish smooth tissue. The lobular arrangement can be distinguished on cross section and these lobules are demarcated by the fine grayish strands. The parenchyma has a slightly yellowish color, and fine septal-like strands of gray tissue interlace in the yellowish parenchyma. The uterus is 4.5 cm. long. The surface is normal. On cut section the endometrial cavity is small, but the endometrium is distinct. The myometrium contains one large circumscribed mass 1 cm. in diameter and multiple small nodules ranging from 2 to 4 mm. in diameter. It has a striated appearance. The tubes are normal. The right ovary is small, measuring 2.5 by 1.25 by 1 cm. The surface is smooth, and on section an occasional small white scar is noted. There are no cysts of corpora lutea.

"Blocks of tissue are fixed in Zenker's fluid with acetic acid, and 10 per cent formalin.

"Microscopic examination of the ovarian tumor shows it to be composed of fibroblasts arranged in bundles and fascicles (Fig. 4). In some regions the cells are compactly placed; whereas, in other parts they are loosely arranged. The nuclei are long and slender and have diffusely scattered small chromatin granules and fine chromatin threads. An occasional mitotic figure is present. The cells in compact regions are not clearly outlined. Fine collagenous fibrillae are present between the nuclei. In the less compact areas the nuclei are separated by fibrillae, in some places tightly packed, in other places loosely arranged. Small vascular channels are present throughout. The capsule of the tumor is composed of laminated layers of collagen. Connective tissue stains, particularly Mallory's phosphotungstic acid hematoxylin and Mallory's acid fuchsin aniline blue, bring out the collagenous nature of the fibrillae of the cells of the tumor.

"Sections of the tubes show no significant alterations. On the peritoneal surface there are several minute epithelial-lined cysts which are probably embryonic remnants. Sections of the other ovary show a compactly arranged cortical stroma with no primordial follicles. There are a few scattered corpora albicantia deep in the medullary portion.

"Sections of the uterus show a thin irregular endometrium composed of glands that vary in size, shape, and location. Many are cystic; others have the ordinary tubular form. The stroma is compact and fibrous. Throughout the myometrium are islands of endometrial stroma and epithelial lined glands. There is a diffuse increase in interstitial fibrous tissue. The combination of the endometrial islands and increased fibrous tissue stroma produced the striated gross appearance of the uterus."

*Diagnosis.*—(1) Fibroma of the left ovary, (2) atrophy of the right ovary, (3) normal tubes, (4) adenomyosis of the uterus, single leiomyoma of the uterus, atrophy of the endometrium.

#### COMMENTS

Certain aspects of this case are of interest and have not been previously emphasized in connection with this unusual syndrome. The microscopic findings of the centrifuged pleural fluid (Fig. 2), showing a distinct nest of cells in acinar arrangement, may be of significance in relation to the unexplained problem of why pleural effusion occurs in these ovarian fibromas.

The fact that this patient had been given a thorough course of radiation therapy to her pelvis on the assumption that the tumor was a uterine fibroid would tend to show the ineffectiveness of radiation therapy as treatment for a benign fibroma of the ovary.

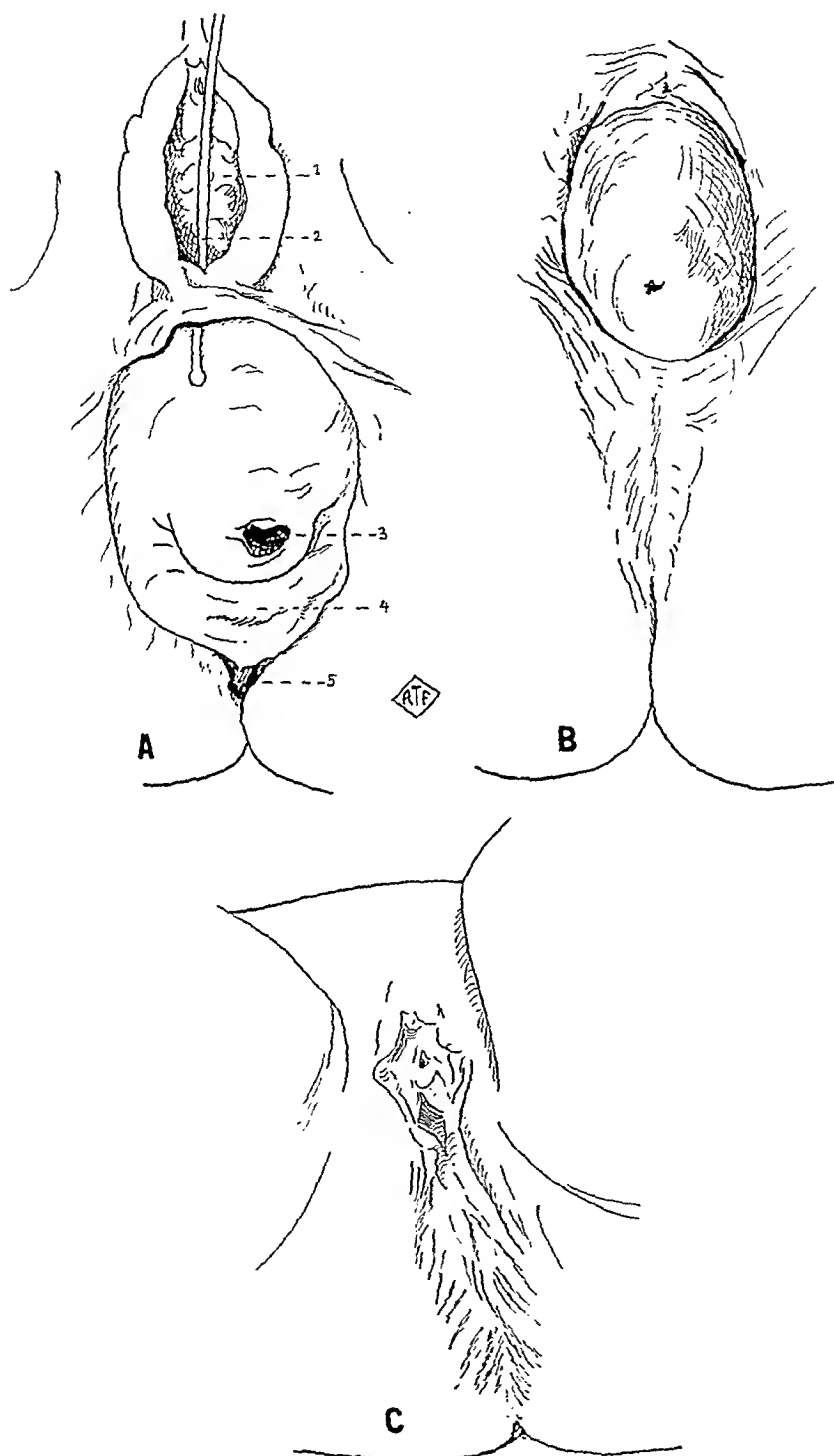


Fig. 1.—View in lithotomy position. *A*, prolapse and enterocele after second operation: 1, anterior vaginal wall; 2, probe inserted under skin bridge representing remains of perineum; 3, prolapsed cervix (external os); 4, posterior traumatic enterocele; 5, skin opening of sinus tract. *B*, Condition after fifth operation: Enterocele cured. Prolapse of cervical stump and eversion of vagina. *C*, Final result with patient straining. (Redrawn from photographs.)

## CASE OF POSTOPERATIVE PELVIC ENTEROCELE AND UTERINE PROLAPSE

ROBERT T. FRANK, M.D., AND RALPH COLP, M.D., NEW YORK, N. Y.  
(From the Surgical and Gynecological Services of the Mount Sinai Hospital)

A UNIQUE traumatic perineal enterocele, complicated by prolapse of the cervix with eversion of the vagina, developed in the course of treatment in a patient in whom a rectal carcinoma had been operatively removed. The condition itself is of interest because of its rarity. The major interest, however, centers in the final operative cure of the condition, because of the many anatomical defects and technical complications which had to be overcome.

CASE REPORT.—Mrs. P. S., aged 52 years, gravida iv, para iii, a widow, was admitted to the Mount Sinai Hospital, on the service of one of us (R. C.). For thirty-four years she had suffered from bloody stools and diarrhea. Nineteen years previously an appendicostomy was established for treatment of the large bowel. Eleven years ago the opening closed spontaneously. This was followed by intestinal obstruction in a postoperative ventral hernia and was relieved by operation.

The present history shows a continuation of the bloody stools and diarrhea. There was a loss of ten pounds and recently also oligomenorrhea.

Physical examination showed a large, obese woman. The lower abdomen was occupied by a solid mass. Rectal examination showed an annular constriction of the rectum, above the sphincter ani. The heart, lungs, and kidneys appeared normal. Biopsy from the rectum showed an infiltrating carcinoma.

*First Operation, First Stage Lahey (R. C.) (April 15, 1936).*—The sigmoid was divided between clamps. A permanent colostomy was established in the left rectus muscle, the end of the distal sigmoid loop implanted through a suprapubic stab wound. At this operation it was found that the liver and abdomen showed no signs of metastases. A fibroid uterus which filled the pelvis was left undisturbed.

*Second Operation, Perineal Resection (R. C.) (April 30, 1936).*—The coccyx was removed. The posterior cul-de-sac was opened. A considerable portion of the adherent posterior vaginal wall was resected with the involved lower sigmoid, rectum, and anus. The distal end of the isolated sigmoid loop was closed and buried in the perirectal cavity. Liberal pelvic drainage.

The patient was seen by one of us (R. T. F.) on May 18, 1936, because of a huge vaginal eversion behind the perineum, which was represented by a mere tissue bridge. She was admitted to the Gynecological Service (R. T. F.) on Jan. 10, 1937. Behind the perineal skin bridge was the prolapsed and everted vagina with a hypertrophic cervix and below this the traumatic enterocele. The prolapse occurred through the area which had previously represented the perineal body, anus, and retroanal tissue. (Fig. 1A.)

*Third Operation, Sigmoidectomy of Residual Sigmoid, Supravaginal Hysterectomy for Fibroids (R. C. and R. T. F.) (Jan. 15, 1937).*—The suprapubic stoma which represented the upper end of the remaining sigmoid was circumcised and freed. The peritoneal cavity was opened widely and a supravaginal hysterectomy of a uterus, enlarged by multiple fibroids to the size of a three and one-half months' pregnancy, was performed, the section being high in order to preserve a

both sides they were freed by blunt dissection and sutured together in the median line behind the vagina (Fig. 2B). The lowermost suture was passed through the periosteum of the anterior surface of the sacrum (as shown in Fig. 2C, 2). Residual granulation tissue was removed and a new high "perineum" built up with whatever tissues could be brought together. Posteriorly a gauze drain was inserted to the tip of the sacrum through the skin opening of the fistulous tract. (Fig. 2A, 4.)

Soon after operation a recurrence of the posterior bulge was noted and the cervical stump prolapsed one and one-half inches beyond the vulva. The hernia contained intestine, as could be ascertained by the presence of tympany and intestinal gurgle.

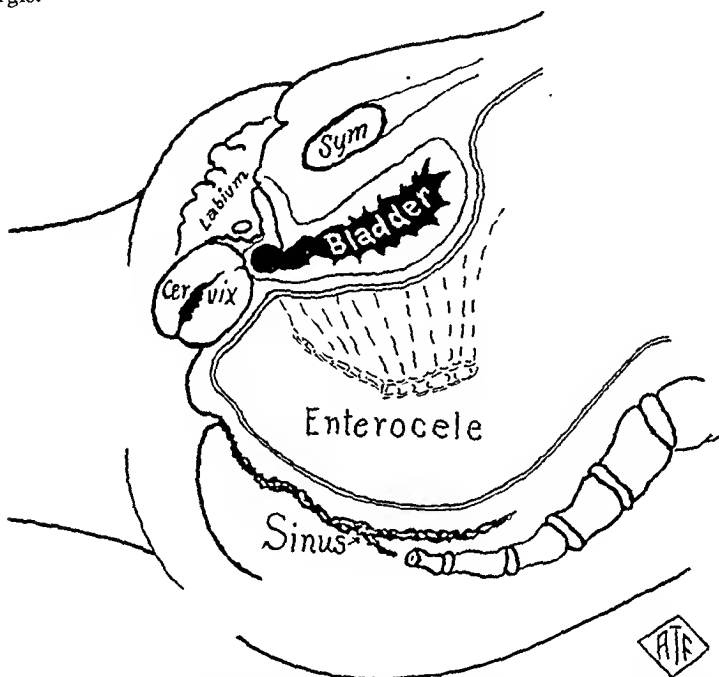


Fig. 3.—Schematic sagittal section of pelvis showing condition before Operation 5. The broken lines indicate position of right half of the partly resected levator plate as viewed through peritoneum and endopelvic fascia.

*Fifth Operation, Plastic Repair of Enterocoele (R. T. F.)\** (June 15, 1938).—A semilunar transverse incision was made behind the vagina. The posterior vaginal wall was separated, mainly by sharp dissection, from the protruding hernia. The peritoneal sac which now was the size of a fetal head, was dissected free from the dense scar anchoring it to the pelvic walls. On opening the huge sac, the posterior surface of the cervical stump and the base of the parametria were visualized. After reducing the protruding small intestine upward, the sac was tied off high up by a circular chromic suture, including anteriorly the posterior surface of the cervical stump, laterally the endopelvic fascia, and posteriorly the peritoneum and fascia along the posterior surface of the Douglas' cul-de-sac. (Fig. 2C.) The levator plates were again brought together below the peritoneum although the approximation entailed greater tension than at the previous operation (Fig. 2B). Below the levator sling all available tissue was again approximated in the median line. A posterior drain was inserted through a lateral stab wound. Fig. 3 is a schematic sagittal section showing the condition before this operation.

long cervical stump. Both adnexae were removed and the cervical stump completely peritonealized as in a typical supravaginal hysterectomy.

The residual sigmoid loop was then completely freed, the pouch of Douglas opened, the sigmoid pushed into the extraperitoneal pelvic cavity, and the peritoneum of Douglas' cul-de-sac reclosed over the bowel. With the patient now in lithotomy position, the sigmoid was completely removed through the reopened perineal incision. A long fistulous tract was excised and the cavity packed.

As the patient had shown no signs of recurrence of the cancer in one year and as the prolapse incapacitated her, a reparative operation was decided upon.

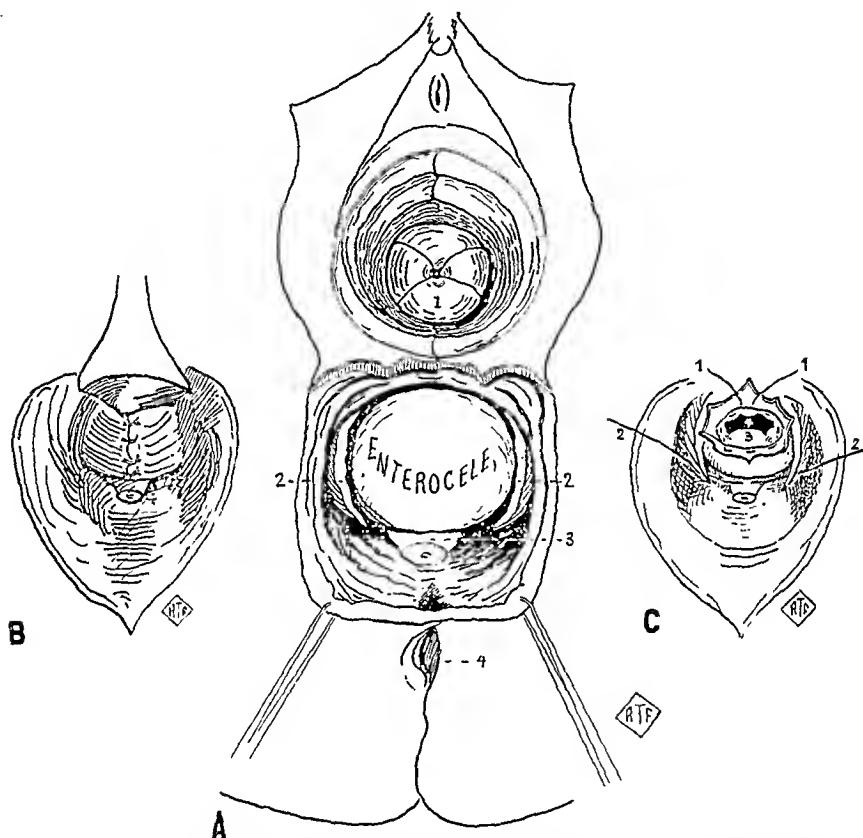


Fig. 2.—Operative procedures (fourth and fifth operations). A, Manchester operation completed. Enterocle exposed: 1, amputated cervix; 2, edges of levators previously resected at Operation 2; 3, lower end of sacrum; 4, skin opening of sinus tract. B, Levator edges united by suture in Operations 4 and 5. C, Enterocle sac opened (Operation 5): 1, ends of pursestring suture used for reclosing hernial sac; 2, ends of lowest levator suture passing through periosteum of sacrum; 3, promontory of sacrum shining through peritoneum of Douglas' pouch; 4, upper peritoneal cavity; the cervical stump is situated above 4.

*Fourth Operation, Manchester Operation for Prolapse, Repair of Traumatic Posterior Enterocle (R.T.F. and R.C.) (April 5, 1937).—*The perineal skin bridge was cut, the bladder freed, and a typical Manchester operation performed with repair of the posterior vaginal wall.

After this stage had been completed and the cervix had receded upward, a transverse incision behind the vagina was made and the subperitoneal pelvic cavity widely opened. The previously partly resected (at Operation 2) levator ani plates were visualized where they had retracted upward and laterally. (Fig. 2A.) On

# THE INDICATION FOR SPLENECTOMY IN THE ASSOCIATION OF ANEMIA AND SPLENOMEGALY

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THE presence of an impoverished condition of the blood is a very common one in clinical medicine. Under certain conditions hypochromic anemia is associated with various grades of enlargement of the spleen and in a certain proportion of the latter another factor becomes apparent which is associated with hemolytic destruction of the red blood cell.

Hemolytic destruction of the red blood cell is not always due to the same factor nor always are the same laboratory evidences present in cases which apparently possess very similar clinical manifestations. Three groups of cases are clinically discernible based upon the reaction of the patient to splenectomy.

*Group 1. Cases in Which the Indication for Splenectomy Is Sharply Defined and in Which a Permanent Good Result ("Cure") Can Be Expected.—*

CASE 1.—A 37-year-old nulliparous female of German birth was admitted on April 14, 1939, because of a progressively increasing menorrhagia of six months' duration, characterized by a gradual lengthening of the menstrual periods from three to fourteen days. She had not observed bleeding from any other part of her body. Even though the appetite was good and there was a sense of well-being, there was a loss of eight pounds in weight. There was no history of tuberculosis, syphilis, malaria, etc.

The previous history was as follows: In September, 1938, the patient returned from a trip to Germany, where she had been subjected to a restricted food diet, because of the rationing system that prevailed. She then visited her family physician because she had noticed a loss of weight and an "anemia." He called her attention to the jaundice which had hitherto not been observed; he was also able to feel a slightly enlarged spleen. Hematologic studies were made on several occasions, including study of the bone marrow, and showed a severe grade of hypochromic anemia, a reticulocytosis, and a spherocytosis; preponderating normoblasts were present in the bone marrow. "There is no doubt that the patient has a congenital hemolytic icterus" (report of Dr. Rosenthal).

In April, 1939, her family physician again saw the patient, at which time there was no subjective or objective relief or subsidence of the symptomatology.

The physical examination on admission revealed a 37-year-old white female, well nourished and not appearing acutely ill. The positive findings were as follows: (1) slightly icteric sclerae; conjunctivae and mucous membranes relatively pale; (2) systolic murmur at the apex; blood pressure, 140/90; (3) a spleen that was enlarged to three fingerbreadths below the left costal margin; (4) no evidence of lymphadenopathy; (5) vaginal examination was essentially negative.

We were all agreed that the patient had a congenital hemolytic icterus and, since the general condition of the patient was eminently satisfactory and she seemed to be in a latent stage, splenectomy seemed indicated.

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The result in regard to the enterocele was good, but a new eversion of the vaginal walls with prolapse of the cervical stump developed (Fig. 1B). This incommoded the patient greatly. The patient, who is a widow, gave her consent for a complete colpectomy.

*Sixth Operation, Colpectomy and Coring Out of Cervical Stump (R. T. F.)\** (Oct. 12, 1938).—The cervical canal was cored out. The flat portio was denuded of mucosa as it was considered essential to leave as much cervical tissue as possible, because the closure of the peritoneal sac at the previous operation was effected partly with these tissues. The vaginal mucosa was removed to within one inch of the urethral meatus and the vaginal canal obliterated by successive layers of circular sutures.

Re-examination of the patient Jan. 12, 1940, three and one-third years after the primary operation, shows a firm perineum without bulge, a functioning left abdominal colostomy, the patient symptomatically and anatomically well (Fig. 1C).

This unusual combination of conditions necessitated six operations for complete re-establishment of health. Before operation the size of the fibroids had prevented a prolapse of cervix and vagina. Excision of the rectum produced marked weakening of the pelvic supports and after hysterectomy, which was essential to permit approach for sigmoidectomy, complete prolapse of the vagina and cervical stump followed. The radical operation required for excision of the carcinoma necessitated division and partial excision of the pelvic diaphragm and thus permitted the huge enterocele to develop.

#### REFERENCE

1. Frank, R. T.: "Parametrial Fixation" (Manchester Operation) for Prolapse of the Uterus, *Am. J. Obst. & Gynec.* 29: 240, 1935.

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\*I (R. T. F.) desire to thank Dr. I. C. Rubin for having extended the courtesy of the Gynecological Ward to me for performing the last two operations.

*Comment.*—Hemolytic jaundice is an inherent, usually familial disease which occurs at any age or in any sex or race and which has no geographic limitations. The basic pathologic change occurs in the red blood cells. They are different in size and shape; are smaller, thicker, and spherical; and the cell assumes a biconvex appearance in contrast to its normal biconcave morphology. These microspherocytes are so typically diagnostic of this condition that the latter is referred to, at times, as "microspherocytosis." The spherocytes are as typical of this condition as the sickle cells are in sickle-cell anemia. The cells are peculiar in that they possess none of the natural ruggedness of the normal biconcave red blood cell and so account for the demonstrable fragility of the latter cell, which becomes one of the diagnostic features of this disease.

No satisfactory explanation exists as to the cause and biologic mechanism of this affliction. It is known that it is more severe on successive transmissions and limited by the death of the more severe types. There are cases in which people possessing a peculiar yellow pallor are vigorous throughout life, but can nevertheless transmit the disease. Splenectomized individuals of this type can transmit the disease.

The splenomegaly is a secondary change which accompanies the increased destruction of red blood cells: the latter leads to a hyperactive bone marrow and an increase in the erythropoietic tissue, and to an outpouring of reticulocytes as well as the granulopoietic elements or leucocytes. The increased destruction of red blood cells explains the higher values of serum bilirubin obtained from the splenic vein as compared to that from the splenic artery. When the demand upon the bone marrow has exceeded its normal capabilities, the bone marrow emits normoblasts, nucleated red blood cells, and immature white blood cells into the circulating blood. This may occur in the presence of infection and a pre-existing hemolytic icterus and is regarded as a "bone marrow crisis" and, clinically, as an acute phase.

The subjective and objective symptomatology results from all of these factors. A number of patients enjoy good health and a normal life and the condition is only detected in the course of a routine examination. Some cases present themselves to the physician because of a "yellow color"; others because of symptoms resulting from anemia or weakness, cold extremities, palpitations, menorrhagia, etc.; or because of the splenomegaly, there are abdominal pains and dragging sensations.

In all typical cases the laboratory findings are conclusive and are as follows: (1) Increased fragility of the red blood cells (normally 0.42 to 0.34 complete; hemolytic anemia, 0.48 to 0.42); (2) variable anemia (3.0 M. to 1.0 M.); (3) color index below 1; (4) a volume index which is normal, or slightly below normal, since the thickness of the red blood cells compensates for any diminution of its size; (5) leuco-

On April 8, 1939, I explored the patient under avertin-gas-oxygen anesthesia and found the following: a markedly enlarged spleen, an absence of any accessory splenic tissue, a normal appearing liver, an extrahepatic biliary tract which was normal to palpation, no fluid in the abdominal cavity, normal pelvic organs with the exception of an immaterial, slight cystic condition in one ovary. Specimens of blood were aspirated from the splenic artery and the splenic vein for study. A rather easy splenectomy was done; a biopsy of the liver was taken from its left lobe and the abdominal wound was then closed without drainage.

Even though the patient bore the operation very well, a transfusion of 500 c.c. of blood was immediately given by the citrate method. Thereafter the patient made an uninterrupted and uneventful recovery and was discharged from the hospital thirteen days after operation.

We inquired carefully into the family history and discovered that the patient had one brother living in Germany who seemed to have a somewhat similar condition, for which, recently, he has also been operated upon.

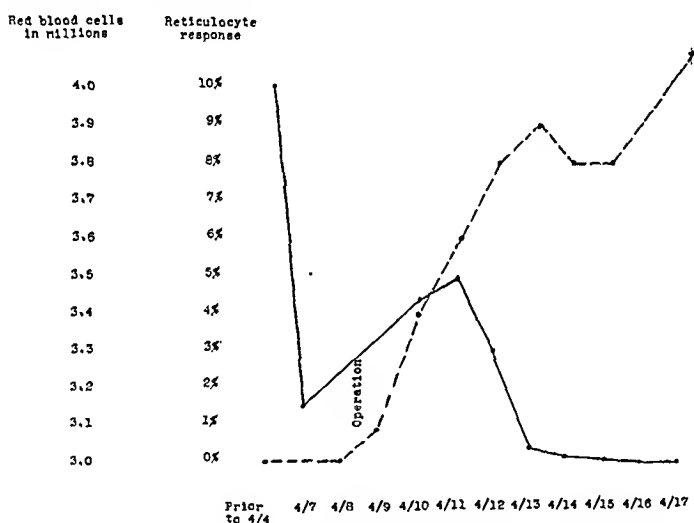


Fig. 1.—Red blood cell and reticulocyte response preoperatively and postoperatively.

An analysis of the diagnostic hematologic work-up shown in Table I and Fig. 1 is as follows: (1) The correction of the hypochromic microcytic anemia to the normal; (2) diminished cell volume in the blood; (3) temporary persistence of microcytosis after operation; (4) normal platelet counts; (5) disappearance of the reticulocytosis after operation; (6) the persistence but lessening of the fragility of the red blood cells after operation; (7) the slight leucocytosis which was present after operation; (8) normal blood chemistry, bleeding and coagulation times; prothrombin time slightly increased; (9) a direct and indirect van den Bergh indicating both obstructive and nonobstructive elements; bromsulphalein test indicating some liver damage; (10) a relative equality of the bilirubin value for blood from the splenic artery and vein; (11) disappearance of urobilinogen present before operation.

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TABLE I

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TABLE II

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cytoses; (6) reticulocytoses (may go as high as 50 per cent); (7) microcytoses; (8) spherocytosis (this is diagnostic).

Of all of these factors the outstandingly important one concerns the physical characteristics of the red blood cell; that is, the spherocytosis. This does not occur in all cases of hemolytic icterus, but when it does occur it forms the positive indication for splenectomy. However, in any "crisis" conservative treatment, including iron, high caloric diet regulation, and repeated transfusions, is temporarily indicated. The splenectomy, nevertheless, should be done only in latent periods and after due preparation. In successfully splenectomized cases the results are spectacular and show at once. The operative result is followed by what is, in effect, a permanent remission of the disease since microcytosis, sphericity, and the increased fragility of the red blood cells may persist. However, marrow activity is decreased, a rise in the hemoglobin and a rise in the red blood cell count level occur with a diminishing reticulocytosis until a normal cellular level is obtained.

CASE 2.—In a young male patient, 17 years of age, there was a history of severe post-tonsillectomy hemorrhage ten years previous to the present admission followed at later times by severe hemorrhage after the extraction of teeth, episodes of severe epistaxis, and the appearance of recurrent bleeding red spots on the fingers of the right hand. The patient was admitted because of uncontrollable hemorrhage from the nose of three days' standing.

Except for cutaneous purpura, the physical examination was essentially negative. The laboratory hematologic work-up is shown in Table II.

The hematologic diagnosis was: Thrombocytopenic purpura hemorrhagica. As the patient was in a chronic phase of the affliction, splenectomy was advised and performed. The operative findings included a somewhat enlarged spleen and a small accessory spleen; both of these were removed.

The postoperative laboratory hematologic observations are also shown in Table II.

There was no further bleeding of any kind after the splenectomy, the patient made an uneventful convalescence and was discharged from the hospital "well."

The patient has been followed since then. There has been no further tendency to bleed. He has gone through operations for subacute appendicitis and for the removal of a pilonidal cyst without any difficulty. Several times he has been readmitted to the hospital for episodes of unclassifiable abdominal pain without any signs of bleeding, from all of which there has been spontaneous and satisfactory recovery.

*Comment.*—In cases of thrombocytopenic purpura hemorrhagica of congenital origin and/or of long standing the demonstrable depletion of the platelets is the indicating sign for splenectomy. In the acute or critical periods of the disease splenectomy is ill advised and is sometimes followed immediately or within a relatively short time by a fatality. Splenectomy is indicated only in the long-standing chronic cases and should be done if possible in periods of remissions; nevertheless, it is also unsurpassed as a method of hemostasis in critical periods of bleeding.

TABLE III

[illegible]

Cessation of all bleeding in properly selected cases is to be immediately expected and does occur; and, when no other supply of splenic tissue exists, cessation becomes permanent. The importance of looking for and removing all accessory splenic tissue is, therefore, paramount, and the unfortunate heedlessness, default, or omission of the removal of the latter probably accounts for all cases of failure after splenectomy done for this indication.

In such cases, of which the described case is a good example, the defect is unassociated with any other form of demonstrable pathology, the clinical concept of thrombocytopenic purpura hemorrhagica becomes a self-contained and sufficient entity, and recovery becomes permanent.

*Group 2. Cases in Which the Indication for Splenectomy Is a Symptomatic One and Is Justifiable in Order to Relieve the Tendency to Bleed, but in Which the Underlying Disease Is Uninfluenced by the Removal of the Spleen.—*

CASE 3.—A young man of Italian parentage, whose grandfather is said to have had similar bleeding episodes, came to the hospital with the history that from the age of 6 years he had been subject to: (1) frequent epistaxis lasting several hours, especially in winter; (2) alarming episodes of bleeding lasting from two to three days following any tooth extraction; (3) very excessive ecchymosis following even slight trauma; (4) overprominent abdomen, as a child causing his friends to call him "sparrow belly."

Because of these symptoms he was studied at another hospital about six months previously where a diagnosis of purpura hemorrhagica was made. Radiologic studies made at that time showed no changes in the long bones or in the skull. Except for this bleeding tendency the patient has had no symptoms of any kind referable to any part of the body, and he has continued to look relatively well up to the present time.

Several months ago following trauma to the thigh an especially large subcutaneous hemorrhage developed and because of this and because of continuing nosebleeds and because he himself felt a mass in the abdomen he came to the hospital for treatment.

The patient was a tall, thin, pale, light olive complexioned man whose general physical examination was essentially negative. There was no enlargement of the lymph glands anywhere in the body. No petechiae or ecchymosis were visible and there was no evidence of bleeding about the gums. In both of the eyes there was a slight heaping-up of the conjunctiva, suggestive of a pinguicular formation. There was a soft systolic murmur at the apex.

The entire left half of the abdomen was occupied by a large nontender mass which was evidently a greatly enlarged spleen. The liver was palpable about one-half inch below the costal margin. There was no ascites.

Under diagnosis of thrombocytopenic purpura I explored the patient and noted the following: no excess bleeding on entering the abdomen; no ascites; the spleen occupied the entire left half of the belly and a small accessory spleen about one-half inch in diameter was present near the tail of the pancreas. Except for some enlargement, the liver looked normal. No enlargement of the abdominal lymph nodes



TABLE IV

DATE	PLATELETS	% HEMOGLOBIN	RED BLOOD CELLS	WHITE BLOOD CELLS	POLYCHROMOPHONUCLEAR	BAND FORMS	LYMPHOCYTES	MONOCYTES	BLEEDING TIME IN MINUTES	COAGULATION TIME IN MINUTES	STOOL	TRANSFUSIONS (CITRATE) C.C.	MISCELLANEOUS*
5/17/39	50,000	75	3,940,000	15,100	53	30	7	6	7	4	+		Reticulocytes: 0 Blood culture: negative Clotting retraction: normal Reticulocytes: 0.5 Spinal tap: negative Rumpel-Leede test: negative Reticulocytes: 0 Moccasin venom: 0.1 c.c. of 1:3,000
5/18/39	80,000	54	2,680,000	10,500	58	11	25	0	4	3½	+		
5/19/39	24,000	38	2,210,000					8	6	3	+	300	
5/20/39		43	2,440,000	3,200	60	12	20						
5/21/39		52	2,250,000	4,000	47	26	22	3					
5/22/39	50,000	44	2,210,000	3,900	57	4	20	14			+	250	
5/23/39	65,000	46	2,340,000	4,700	63	3	18	11	2½	3½	+	300	Moccasin venom: 0.2 c.c. Spinal tap: negative except for sugar, 90.1 mg. %
5/24/39	25,000	43	2,350,000	7,000	62	7	15	16			+		Blood culture: sterile
5/25/39	20,000	40	2,180,000	11,400	76	3	12	8			+		
5/26/39	60,000	38	2,180,000	14,600	76	2	13				+	300	

\*Urine negative throughout.

Hippuric acid: 1.96 Gm. excreted No parasites in stool									
5/27/39	60,000	52	2,620,000	12,300	77	7	12	4	300
5/29/39	50,000	32	1,960,000	10,500	68	8	10	6	
6/1/39	50,000	48	2,710,000	5,100	58	5	26	7	
6/3/39	50,000	45	2,510,000	5,300	57	4	24	13	300
6/6/39	110,000	55	3,500,000	8,500	48	3	32	14	
6/9/39	70,000	50	2,600,000	3,800	72		25	3	300
6/12/39		60	3,350,000						
6/13/39	Operation: ethyl chloride-ether 2:25 P.M.-3:15 P.M.								
6/13/39	50,000	72	3,730,000	22,500	70	12	6	11	350
4:15 P.M.	90,000	85			28	6	53	6	
	Splenic vein								
6/14/39	140,000	92		16,700	79	2	7	11	
6/16/39	180,000	88		17,300	81	2	8	8	
6/17/39	180,000	90		11,600	74	2	7	11	
6/18/39									
6/20/39	270,000	76		117,000					
6/23/39	280,000	84							
6/24/39	290,000	86							
6/26/39	290,000	80							
6/28/39	270,000	90	4,800,000	12,300	26	3	61		
6/29/39									
6/30/39									
7/3/39	440,000	86							
7/11/39	370,000	82							

Eosinophiles: 4  
Basophiles: 1  
Myelocytes: 1  
Türk cell: 1

Serum bilirubin: 0.5 u/100 c.c.

Blood culture sterile

Blood smear negative for malaria

Blood smear negative for malaria

Blood culture sterile

Blood chemistry: glucose, 64.9; N.P.N., 26.5; uric acid, 3.5; creatinine, 1.21

was present. The spleen and necessary spleen were removed and a biopsy was taken from the liver. Specimens of blood were also taken from the splenic artery and splenic vein.

The patient made a very uneventful convalescence and was discharged from the hospital approximately two weeks after being operated upon.

*Comment.*—The entire hematologic laboratory work-up both before and after operation is shown in Table III. The diagnosis made before operation was thrombocytopenic purpura, which we were entitled to make from the available data. When the spleen was removed, it did not look typically that of a thrombocytopenic spleen, especially because of its size and because of the peculiar nodules which were present throughout the spleen. The anatomical diagnosis was Gaucher's disease inasmuch as typical foamy cells were found in both spleen and liver. When we looked at the conjunctiva there was no doubt that there was present a slight heaping-up of fat at the outer margin of the cornea, but the lesion was not very marked and I am quite sure that many normal individuals might show a similar slight heaping-up of fatty tissue.

In view of the bleeding tendency and the diminished platelet count indicating a condition of thrombocytopenic purpura, the indication for splenectomy is quite well marked, and justifiably so; this is borne out by the subsequent history, which up to the present is marked by total disappearance of the bleeding tendency. It seems unnecessary to emphasize, however, how little this will influence the underlying Gaucher's disease in which the thrombocytopenic purpura is an incidental symptom in a much more important systemic disease.

*Group 3. Cases in Which the Indication for Splenectomy Is a Doubtful One and the Outcome Unpredictable and the Operation Is Commonly Done in the Absence or the Unavailability of Any More Conservative (Medical) Form of Therapy.*—

CASE 4.—The fourth patient was a young boy, 7 years of age, who came to the hospital during a febrile episode with a history that he had appeared ill and lethargic for the prior four days. A "sore" throat was present on the day before admission. He had vomited several times in the past four days, the last vomitus containing blood. There was indefinite abdominal pain, no cough, no hemoptysis, no loss of weight, and no history of having swallowed any chemical or foreign body. Although the patient appeared acutely ill, the general physical examination was essentially negative. There was no rash, no ecchymosis, no petechiae, no evidence of bleeding from the gums. Nevertheless, during the examination he vomited about 200 c.c. of partially clotted, dark blood. There was a slight diastolic blow at the apex. The abdomen was relaxed, although there was some definite muscle defense spasm. The spleen was easily palpable three fingerbreadths below the costal margin. The liver was not palpable. Except for a few inconsequential nodules in the axilla the rest of the lymphatic system was negative. The patient's temperature persisted for about two weeks after which time it came down to normal. The condition of the liver and spleen persisted up to the time of operation. In view of the hematologic work-up (Table IV) a diagnosis of either Banti's disease or thrombocytopenic purpura was made and it seemed indicated to do a splenectomy.

A splenectomy was done thirty-one days after the onset of the symptoms. A small amount of clear fluid was found in the abdomen. The liver looked normal. The spleen was enlarged down to the umbilicus, and there were several small masses of accessory splenic tissue. The spleen and all the accessory splenic tissue were removed in one mass, and a biopsy of the liver was taken.

During the second week after operation there was quite a temperature reaction, but shortly this disappeared and thereafter the patient made an uneventful recovery and was discharged from the hospital well. The pathologic study was made by Dr. J. Felsen, who reported: "Sections of the spleen show a fairly good preservation of normal architectural arrangement. The periarterial lymph nodules are intact. The sinusoids are dilated and in one slide there is a central area of hemorrhagic infarction. Biopsy of the liver reveals linear and focal accumulations of round cells which are rather striking in that they occur chiefly at the periphery of the liver lobules. There is some cloudy swelling of the parenchyma. The picture suggests possible leucemia."

*Comment.*—The fourth case is presented because of the indefiniteness of the manifestations and impossibility of definitely classifying the essential lesion. It may be that the term Banti's disease is appropriate from the standpoint that the modern conception of Banti's disease is that of a terminal entity which results from a number of related or essentially differing preceding conditions. In the absence of any sharply demarcating signs, symptoms, or laboratory facts, the indication for splenectomy is an empiric one and is not as well founded as under other more well-defined circumstances. The outcome in such cases after a successful splenectomy cannot be foretold and must be awaited in hopeful expectancy. Since operation this patient has done reasonably well and has had no complaints, but continued observation over a long time is necessary before any definite opinion can be vouchsafed.

#### SUMMARY AND CONCLUSIONS

In the present state of clinical knowledge the indication for splenectomy in the clinical association of splenectomy and hypochromic anemia exists only under two conditions: (1) when in a person the subject of a hemolytic icterus spherocytes are demonstrable in the circulating blood; and (2) when in purpuric conditions the number of platelets in the peripheral blood is at a very low level. Under such conditions the operation is best done during a remission period, and when so done a good result is to be expected.

# AN INSTRUMENT FOR VISUALIZING THE INTERIOR OF THE COMMON DUCT AT OPERATION

## PRELIMINARY NOTE

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THE problem of locating and removing all the stones in the common duct at the time of operation may be a difficult one. This is particularly true if multiple stones are present near the ampulla. Detection of the stone usually rests on the well-known maneuvers of probing the duct, or palpation, or a combination of the two. If these procedures are felt to be inadequate, the duct may be injected with some radiopaque medium at the time of operation and x-ray films taken to visualize the presence of a stone or other obstruction. This latter method at best may be cumbersome and time consuming, and occasionally presents difficulties in interpretation of the roentgenograms.

With a view to obtaining a more satisfactory method of approaching this problem, an instrument has been designed which may be inserted into the common duct at the time of operation, enabling one to inspect the interior of the duct. The instrument (the general form of which is shown in Fig. 1) consists essentially of a right angle observation telescope, a lighting and an irrigating system.\* Preliminary observations were made on the cadaver to determine the optimum size for the instrument and its possibilities for visualizing foreign bodies in the duct. Fig. 2 was taken through the instrument and shows a stone lying in the common duct (the stone inserted into the lower end of duct of a cadaver).

The dimensions of the present model of the instrument are as follows: The upright portion is 1 cm. in diameter and 45 cm. in length, which allows observation from a distance sufficient to avoid the danger of soiling the operative field. The connections for battery and water are placed somewhat more than 9 cm. from the eyepiece, in order to avoid contaminating the hands during the use of the instrument. The right angle portion, which is inserted into the duct, is about 7 cm. in length and 5 mm. in diameter.

The instrument is used as follows. At operation, after careful palpation, the common duct is opened between two traction sutures in the usual manner. After testing the lighting and irrigating systems, the tip of the instrument bearing the light is passed downward in the duct. While the tip is being introduced, the index finger may be placed over the heel of the instrument (the junction of the upright and horizontal portions) in order to facilitate the insertion of the instrument and also

\*The optical system was devised by Mr. Frederick C. Wappler, of the American Cystoscope Makers, Inc., New York City.

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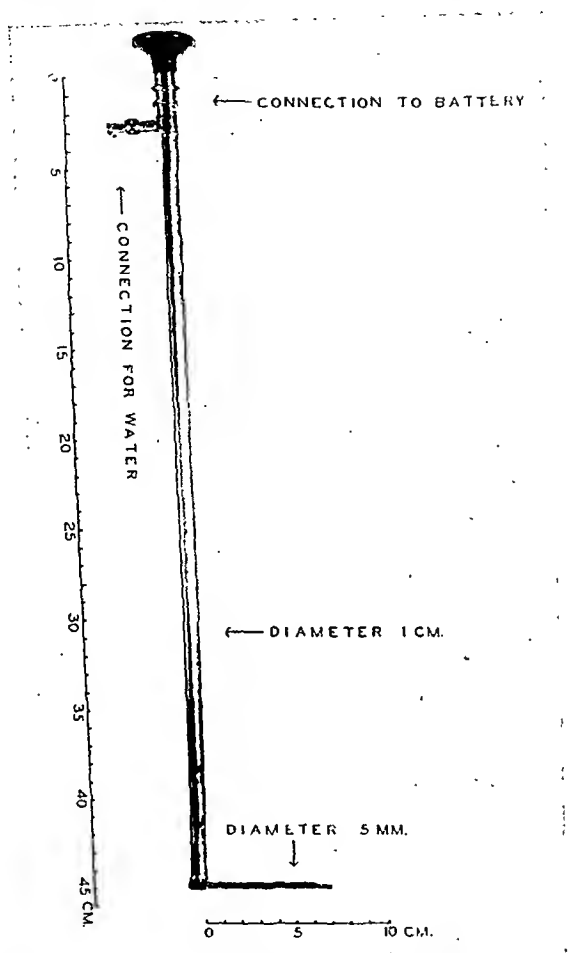


Fig. 1.—The choledochoscope.



Fig. 2.—Photograph taken through the choledochoscope, showing stone lying in the lower end of the common duct (stone inserted into the common duct of a cadaver).

to protect the liver. After the instrument has been introduced, it is desirable to turn off the main operating room light during the period of observation, but further darkening of the room is not necessary. It is essential, in order to obtain a clear vision, that the bile be thoroughly washed out by means of the irrigating system attached to the instrument, and it is desirable to maintain the flow of fluid while inspection is being carried out. After viewing the lower end of the duct, the instrument may be withdrawn and reintroduced for visualization of the upper portion of the duct.

Where the duct is greatly distorted by inflammatory processes, it might perhaps be difficult or even impossible to insert the instrument, but I have personally had no difficulty and have found that no larger opening in the duct is required than that customarily made for passing the usual instruments. The total time required for observation in a simple case need be only a few minutes.

# Recent Advances in Surgery

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CONDUCTED BY ALFRED BLALOCK, M.D.

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## PROGRESS IN SURGERY OF THE AUTONOMIC NERVOUS SYSTEM IN 1938 AND 1939

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IT IS of particular importance for the clinical investigator and the neurosurgeon engaged in problems of vascular, secretory, and viscerai innervation to have a broad understanding of recent developments in neuroanatomy and neurophysiology. Such basic knowledge is essential for the development of successful therapeutic procedures in visceral disease. An understanding of the anatomical arrangement of the autonomic system in the brain stem and spinal cord and of the physiologic effects of irritant and destructive lesions in these areas is also of considerable value in neurological diagnosis and in the avoidance of serious complications which may follow neurosurgical operations. It is for these reasons that so many contributions from the physiologic laboratories are included below.

### ANATOMY AND PHYSIOLOGY

*Cerebral and Hypothalamic Centers.*—Our understanding of the function of the higher centers in the control of the autonomic nervous system has been greatly extended in the last two years. This work has been summarized by Fulton.<sup>1</sup> He points out that autonomic activities are integrated by the central nervous system according to the principle of functional levels. At the spinal stratum only simple vasomotor and sexual reactions can be demonstrated. At the medullary level reflexes are mediated for the maintenance of a constant blood pressure and oxygen supply. Other complex combined reactions of the autonomic and somatic spheres are also located at this level, such as deglutition and vomiting. Integration in the hypothalamus becomes very complex, as this is the principal control center of the autonomic system (see below). The cortex has a rich and varied representation of autonomic activities for the harmonious integration of somatic and viscerai functions. According to Crouch and Thompson,<sup>2</sup> the cortex affects the viscerai mechanisms as a whole rather than affecting the parasympathetic or sympathetic system from isolated areas. The active areas are largely limited to the motor and premotor regions. The effect of stimulating

these areas depends largely on the physiologic state of the organism and the cortex at the time of stimulation. The difference in species also seems to play an important role, the type of reaction being predominantly parasympathetic in the dog and sympathetic in the cat. Pinkston and Rioch<sup>7</sup> have shown that central mechanisms for vasomotor control are localized in the motor and premotor areas (Brodmann's Areas 4 and 6). Bard,<sup>4</sup> who has studied the influence of the cortex on subcortical levels for a number of years, has given a valuable summary of this important work. His conclusions are based on a study of the behavior of animals surviving complete removal of the cortex. Decortication brings out the inhibitory action of the cortex on the lower centers and shows that, with the possible exception of the full display of pleasure, the expressions of such basic emotions as anger, fear, and sexual excitement are effected by mechanisms which are suprabulbar and subcortical. Although these experiments were conducted on animals which stand in the middle third of the mammalian phylogenetic scale, Bard believes that these centers still govern emotional reactions in man, even after the extensive corticalization of function which has taken place in the long period of evolution.

The demonstration that the most important vegetative centers are situated in the diencephalon, grouped around the walls of the third ventricle, the anterior commissure, and the tuber cinereum, began with the experiments of Karplus and Kreidl thirty years ago. It has culminated in the work of Ranson and his school in Chicago. These investigations have been summarized by Ranson and Magoun<sup>5</sup> and the entire subject discussed at a symposium by the Association for Research in Nervous and Mental Disease during a two-day meeting last December. In the proceedings of the Association<sup>8</sup> an effort has been made to correct the wide discrepancies in terminology by following a précis of anatomical terms. This closely follows Clark's nomenclature in the English monograph on the hypothalamus.<sup>7</sup> Evidence obtained from stimulation of discrete areas in the hypothalamus by Ranson and Magoun<sup>5</sup> indicates clearly that the sympathetic discharge originates in the paraventricular areas; there is less conclusive evidence that the more rostrally situated preoptic and supraoptic nuclei are concerned with the parasympathetic division. The latter area in addition gives off a well-defined tract to the posterior lobe of the hypophysis and is of great importance in the control of the antidiuretic hormone and thereby of renal secretion.

The elusive problem of the location of the descending autonomic fiber tracts has been partly cleared up by Magoun.<sup>6</sup> This work, performed in Ranson's laboratory, was carried out by placing lesions along the brain stem with the Horsley-Clark stereotaxic instrument and then observing whether the characteristic pressor responses normally obtained on hypothalamic stimulation were abolished. Evidence was obtained

that the autonomic pathway descends in both the central and tegmental portions of the midbrain. In the pons these fibers are more concentrated in the tegmental region and in the medulla they lie chiefly in the lateral portion of the reticular formation. This coincides with clinical observations recorded by List and Peet,<sup>8</sup> who studied abnormalities in sweating in patients with lesions of the brain stem, and also with evidence secured by Foerster, Gagel, and Mahoney<sup>9</sup> from studies of tumors in this region. From the medulla the pathway enters the anterolateral column in the upper cervical cord. This also has been corroborated in man by Foerster, who observed an ipsilateral Horner's syndrome and diminished sweat secretion after high cervical section of the spinothalamic tract. Foerster also ascribes the fall in blood pressure and loss of vasoconstrictor reflexes after bilateral high cordotomy to interruption of this tract. According to Harrison, Wang, and Berry,<sup>10</sup> hypothalamic impulses may descend to the spinal cord uncrossed or may cross in the brain stem or in the spinal cord below the cervical segments.

Ranson's<sup>6</sup> method of selective destruction of the anterior or the lateral hypothalamic nuclei has shown the role of these centers in the regulation of body temperature. When this area of the brain is heated, heat elimination is increased by an acceleration in the rate of respiration, panting, and sweating of the footpads.<sup>11</sup> These results are interpreted as indicating that this region contains centers which are activated by rising temperature of the blood and that their stimulation leads to elimination of excess heat. Of particular importance to neurosurgeons are the observation in animals that hyperthermia of central origin is reduced by the barbiturates and the suggestion that large doses of these drugs be given when a dangerously high fever follows operative intervention in these areas. Some remarkable instances of loss of temperature regulation associated with small circumscribed tumors in the hypothalamic area have been described by Davison<sup>6</sup> and Zimmerman.<sup>6</sup> Of further clinical interest is the microscopic study of the hypothalamic nuclei in individuals who have died of heatstroke. Morgan and Vonderahe<sup>12</sup> have observed significant evidence of cellular destruction in the exact areas which regulate temperature control.

The effects of hypothalamic stimulation on gastrointestinal activity are reported by Sheehan.<sup>6</sup> Stimulation of the lateral nuclei is followed by inhibition of peristalsis and decrease of muscle tone, with reduced secretion of gastric juice and an increase in mucous content. There is also some evidence that stimulation of the supra- and preoptic areas produces motor responses and an increased acidity of the gastric juice, but this has not been a consistent finding. Sheehan also points out that extensive destruction of the diencephalon is followed by mucosal hemorrhage and erosion in about one-third of all experiments, and that these complications occur much more frequently than after injury to any

these areas depends largely on the physiologic state of the organism and the cortex at the time of stimulation. The difference in species also seems to play an important role, the type of reaction being predominantly parasympathetic in the dog and sympathetic in the cat. Pinkston and Rioch<sup>3</sup> have shown that central mechanisms for vasomotor control are localized in the motor and premotor areas (Brodmann's Areas 4 and 6). Bard,<sup>4</sup> who has studied the influence of the cortex on subcortical levels for a number of years, has given a valuable summary of this important work. His conclusions are based on a study of the behavior of animals surviving complete removal of the cortex. Decortication brings out the inhibitory action of the cortex on the lower centers and shows that, with the possible exception of the full display of pleasure, the expressions of such basic emotions as anger, fear, and sexual excitement are effected by mechanisms which are suprabulbar and subcortical. Although these experiments were conducted on animals which stand in the middle third of the mammalian phylogenetic scale, Bard believes that these centers still govern emotional reactions in man, even after the extensive corticalization of function which has taken place in the long period of evolution.

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generation of a large part of its preganglionic axones) reacts with increased activity when the remaining efferent connections are stimulated.

An ingenious illustration of the increased sensitivity of visceral and skeletal muscle has been given by Bender.<sup>19</sup> Since the sympathetically denervated pupil dilates with adrenaline and the denervated striated muscles of the face contract with acetylcholine, they may be used as indicators for exogenous and endogenous adrenaline and acetylcholine. In the cat, which reacts to fear with a predominant secretion of adrenaline, the denervated pupil dilates widely, whereas the denervated facial muscle gives but a minimum response. In the frightened monkey the denervated pupil does not dilate unless it is rendered additionally sensitive by cocaine, but the denervated facial muscles contract vigorously. These observations indicate that both parts of the autonomic nervous system are active in each species. The cat, however, is predominantly sympathetic, while the monkey is predominantly parasympathetic in its reactions.

Further implications of the sensitization phenomenon are seen in the peculiar complications which sometimes follow injury to the cranial nerves. Lewy, Groff, and Grant<sup>20</sup> have investigated the pseudomotor responses which occur after injury to the oculomotor, facial, or hypoglossal nerves. The ensuing pseudomotor reactions which occur in the eyelid, whiskers, or tongue can be reproduced by stimulating the mesencephalic root of the trigeminal nerve. An autonomic discharge spreads over the nerve, resulting in a slow tonic contraction of the denervated muscles of the eyelid, face, and tongue identical with the effect of acetylcholine injection into the carotid artery of animals so denervated. This probably explains the Marcus-Gunn phenomenon, in which the eyelid is raised when the patient chews, and the Heidenhain and Vulpian phenomena, in which the lip and tongue, respectively, contract when the second trigeminal division in the first case and the chorda tympani or lingual nerves in the second case are stimulated. Another peculiar autonomic disturbance, the phenomenon of "crocodile tears," which may occur on eating after injuries to the facial nerve, is ascribed to aberrant regenerating fibers, so that some of the autonomic fibers which once entered the chorda tympani nerve in their course to the salivary glands become misdirected and reach the lachrymal gland (Ruskin<sup>21</sup>).

The importance of the autonomic nervous system in the mechanism of accommodation has recently been described by Cogan.<sup>22</sup> His paper, which covers a field to which scant attention has been paid and which contains a valuable bibliography, should be of great interest to the surgeon as well as to the ophthalmologist, because a number of patients complain of mild visual disturbances after cervical and upper dorsal sympathectomy. Cogan concludes that stimulation of the sympathetic fibers flattens the lens and accommodates the eye to distant objects,

other part of the brain. Attention was often directed by Cushing to gastrointestinal complications in man after operations on the pituitary and third ventricle.

Evidence secured from lower animals cannot always be safely transferred to man, so White<sup>6</sup> was led to repeat the observations on stimulation of the hypothalamic areas in man. This can be done effectively and safely under local anesthesia during drainage operations on the third ventricle for internal hydrocephalus. The cardiovascular responses in five patients were quite similar to those obtained in animals.

*Chemical Mediation of Nerve Impulses.*—Evidence which has been summarized in preceding reviews of this series<sup>13e-h</sup> has brought out with increasing weight the importance of chemical mediation in the distribution of nerve impulses. The argument over electrical versus chemical propagation of the nerve impulse to visceral and skeletal muscle, as well as across interneuronal synapses, has been intense. Recently Cannon<sup>14</sup> has presented evidence which seems to prove conclusively that this process is entirely chemical. A corollary to this phenomenon, which is of great practical importance in the technique of surgical procedures, is the sensitization to adrenaline, sympathin, and acetylcholine which follows nerve degeneration. After summarizing this evidence, Cannon<sup>15</sup> has formulated a Law of Denervation to the effect that, when a series of efferent units is destroyed, increased irritability to chemical agents develops in the isolated structure, the effect being maximal in the part directly denervated. Through sensitization the dose of the chemical substance required to produce a response is less after operation than before. Whereas extreme sensitization results from cutting the ultimate adrenergic fibers (postganglionic section), a moderate sensitization develops after preganglionic section. The practical importance of this phenomenon is illustrated in vascular denervation of the extremities. Striking and long-lasting vasodilatation follows lumbar ganglionectomy in which only preganglionic fibers to the sciatic nerve are cut, but after postganglionic section, such as occurs in injuries to peripheral nerves or in cervicothoracic ganglionectomy, the initial complete relaxation of the vessels is soon followed by the return of a certain degree of vasoconstrictor tone. After injuries to the peripheral nerves this is so pronounced that it accounts in large part for the vasomotor and nutritional changes which may be such a distressing complication (Atlas<sup>16</sup>).

The sensitization effect necessitates a very thorough denervation of a given area, so that the secretion of sympathin at the nerve endings of remaining intact postganglionic axones or of acetylcholine liberated in the ganglionic synapses and adrenal medulla after an incomplete preganglionic sympathectomy will not spread to the denervated but sensitized cells and reproduce the response. Simeone<sup>17, 18</sup> has shown that a partially denervated adrenal gland or sympathetic ganglion (after de-

generation of a large part of its preganglionic axones) reacts with increased activity when the remaining efferent connections are stimulated.

An ingenious illustration of the increased sensitivity of visceral and skeletal muscle has been given by Bender.<sup>19</sup> Since the sympathetically denervated pupil dilates with adrenaline and the denervated striated muscles of the face contract with acetylcholine, they may be used as indicators for exogenous and endogenous adrenaline and acetylcholine. In the cat, which reacts to fear with a predominant secretion of adrenaline, the denervated pupil dilates widely, whereas the denervated facial muscle gives but a minimum response. In the frightened monkey the denervated pupil does not dilate unless it is rendered additionally sensitive by cocaine, but the denervated facial muscles contract vigorously. These observations indicate that both parts of the autonomic nervous system are active in each species. The cat, however, is predominantly sympathetic, while the monkey is predominantly parasympathetic in its reactions.

Further implications of the sensitization phenomenon are seen in the peculiar complications which sometimes follow injury to the cranial nerves. Lewy, Groff, and Grant<sup>20</sup> have investigated the pseudomotor responses which occur after injury to the oculomotor, facial, or hypoglossal nerves. The ensuing pseudomotor reactions which occur in the eyelid, whiskers, or tongue can be reproduced by stimulating the mesencephalic root of the trigeminal nerve. An autonomic discharge spreads over the nerve, resulting in a slow tonic contraction of the denervated muscles of the eyelid, face, and tongue identical with the effect of acetylcholine injection into the carotid artery of animals so denervated. This probably explains the Marcus-Gunn phenomenon, in which the eyelid is raised when the patient chews, and the Heidenhain and Vulpian phenomena, in which the lip and tongue, respectively, contract when the second trigeminal division in the first case and the chorda tympani or lingual nerves in the second case are stimulated. Another peculiar autonomic disturbance, the phenomenon of "crocodile tears," which may occur on eating after injuries to the facial nerve, is ascribed to aberrant regenerating fibers, so that some of the autonomic fibers which once entered the chorda tympani nerve in their course to the salivary glands become misdirected and reach the lacrimal gland (Ruskin<sup>21</sup>).

The importance of the autonomic nervous system in the mechanism of accommodation has recently been described by Cogan.<sup>22</sup> His paper, which covers a field to which scant attention has been paid and which contains a valuable bibliography, should be of great interest to the surgeon as well as to the ophthalmologist, because a number of patients complain of mild visual disturbances after cervical and upper dorsal sympathectomy. Cogan concludes that stimulation of the sympathetic fibers flattens the lens and accommodates the eye to distant objects,

other part of the brain. Attention was often directed by Cushing to gastrointestinal complications in man after operations on the pituitary and third ventricle.

Evidence secured from lower animals cannot always be safely transferred to man, so White<sup>a</sup> was led to repeat the observations on stimulation of the hypothalamic areas in man. This can be done effectively and safely under local anesthesia during drainage operations on the third ventricle for internal hydrocephalus. The cardiovascular responses in five patients were quite similar to those obtained in animals.

*Chemical Mediation of Nerve Impulses.*—Evidence which has been summarized in preceding reviews of this series<sup>12c-h</sup> has brought out with increasing weight the importance of chemical mediation in the distribution of nerve impulses. The argument over electrical versus chemical propagation of the nerve impulse to visceral and skeletal muscle, as well as across interneuronal synapses, has been intense. Recently Cannon<sup>14</sup> has presented evidence which seems to prove conclusively that this process is entirely chemical. A corollary to this phenomenon, which is of great practical importance in the technique of surgical procedures, is the sensitization to adrenaline, sympathin, and acetylcholine which follows nerve degeneration. After summarizing this evidence, Cannon<sup>15</sup> has formulated a Law of Denervation to the effect that, when a series of efferent units is destroyed, increased irritability to chemical agents develops in the isolated structure, the effect being maximal in the part directly denervated. Through sensitization the dose of the chemical substance required to produce a response is less after operation than before. Whereas extreme sensitization results from cutting the ultimate adrenergic fibers (postganglionic section), a moderate sensitization develops after preganglionic section. The practical importance of this phenomenon is illustrated in vascular denervation of the extremities. Striking and long-lasting vasodilatation follows lumbar ganglionectomy in which only preganglionic fibers to the sciatic nerve are cut, but after postganglionic section, such as occurs in injuries to peripheral nerves or in cervicothoracic ganglionectomy, the initial complete relaxation of the vessels is soon followed by the return of a certain degree of vasoconstrictor tone. After injuries to the peripheral nerves this is so pronounced that it accounts in large part for the vasomotor and nutritional changes which may be such a distressing complication (Atlas<sup>16</sup>).

The sensitization effect necessitates a very thorough denervation of a given area, so that the secretion of sympathin at the nerve endings of remaining intact postganglionic axones or of acetylcholine liberated in the ganglionic synapses and adrenal medulla after an incomplete preganglionic sympathectomy will not spread to the denervated but sensitized cells and reproduce the response. Simeone<sup>17, 18</sup> has shown that a partially denervated adrenal gland or sympathetic ganglion (after de-

pathomimetic substances which results (see above). Lewis<sup>30</sup> states that he is "prepared to accept clinical evidence for this conclusion. The preganglionic operation has the merit not only of producing, so it would seem, the greater vasodilatation, but in avoiding the disfigurement of Horner's syndrome." Lewis adds that, even after this improved operation, he can still induce attacks of Raynaud's disease on direct exposure to cold and that the local abnormality remains. In another article Lewis<sup>31</sup> compares the pathologic changes in the arteries of warm-handed people with those in patients with Raynaud's disease. Intimal thickening becomes distinct in both groups with advancing age and is no greater in the mild cases of Raynaud's disease than in the normal controls. This fits in with Lewis' theory of local increased sensitivity to cold. In the more advanced cases with trophic changes in the skin there is intimal hyperplasia, the arterial lumen being greatly reduced or actually occluded by proliferative tissue and organized thrombus. Opposed to Lewis' theory of an entirely local vascular fault are the findings of Day and Klingman.<sup>32</sup> They studied vasomotor reactions in a 6½-year-old girl with acrocyanosis and found that during sleep there was spontaneous warming and reddening of the hands and feet. Local cooling of the hand during sleep did not cause vasospasm. They believe that their study supports the theory of a central rather than a local origin of this abnormal vasomotor tone.

If the dispute over the etiology of Raynaud's disease is still far from settled, the same is true concerning the best method for preganglionic denervation of the upper extremity. Most surgeons agree that cervico-thoracic (stellate) ganglionectomy no longer should be done for vascular disturbances, because the denervated smooth muscle of the arterioles becomes so sensitive to sympathomimetic compounds. Telford<sup>33</sup> and Smithwick<sup>34</sup> each have described a technique for preganglionic denervation of the arm in which the inferior cervical, first and second thoracic ganglia which give rise to the post-ganglionic neurones are left undisturbed, but their central connections are cut. Smithwick's operation through a posterior approach with resection of the third rib would seem to give a better chance to prevent regeneration of fibers from the second and third intercostal nerves. The ability of the sympathetic vasomotor fibers to regenerate is amazing. Simmons and Sheehan<sup>35</sup> tested Telford's series of 38 ganglionectomies and 29 preganglionic sections. They found evidence of relapse in all but 24 per cent of the preganglionic denervations and in all but 10 per cent of the ganglionectomies. In this checkup Simmons and Sheehan state that they took the slightest attack of cyanosis to mean relapse, although the patient may not have attached any importance to it. They also add that the majority of patients after the preganglionic operation were completely satisfied with the result. Therefore they favor the preganglionic operation, saying of it that "clinically they [the patients] are undoubtedly better, the hands never

whereas the parasympathetic aids in focusing on objects at close range. The effect of sympathectomy is not sufficient to make the subject obviously myopic, but the condition is usually detectable by optometric tests.

In addition to the articles on the special subjects which have been covered above, there is a vast number of papers of anatomic and physiologic interest. The reader who is concerned with these fields should read the recent review by Hinsey.<sup>23</sup>

#### EFFECTS OF SYMPATHECTOMY ON CIRCULATION

*The Carotid Sinus.*—A useful anatomic description of the carotid sinus innervation, accompanied by excellent photographs, has been written by Tehibukmacher.<sup>24</sup> The clinical importance of a hyperactive carotid sinus reflex in producing syncope from bradycardia and peripheral vasodilatation, as well as its etiological role in convulsive seizures, has been so well described in the past that nothing new of importance has been reported. Capps and de Takats,<sup>25</sup> however, have reported two cases in which bilateral denervation of the sinus has been performed. Both of these show a significant postural hypotension, but no elevation of the blood pressure or heart rate as a result of removing these important reflex mechanisms for cardiovascular control. Rovenstine and Cullen<sup>26</sup> have described the anesthetic risks in operating upon patients with an abnormal sinus reflex. They state that digitalis and most of the volatile anesthetics in light dosage sensitize the reflex mechanism. To avoid anesthetic accidents, they recommend routine testing by local compression of the carotid bifurcation before operation. Atropine eliminates the vagal cardiodepressor type of reflex. If an abnormal reflex is produced during operation, it may be recognized by the accompanying circulatory changes. The most urgent and important emergency treatment consists of the injection of procaine at the carotid bifurcation.

*Vasospastic Diseases.*—A monograph on the control of the blood vessels has been written by McDowall.<sup>27</sup> This contains information on all aspects of vascular physiology and is an invaluable textbook for reference. In the same field Kunkel, Stead, and Weiss,<sup>28</sup> and Grant and Pearson<sup>29</sup> have extended our understanding of vasomotor reactions in the limbs by comparing vascular responses in the proximal and distal portions of the extremity. Both sympathetic stimuli and adrenaline, as is well known, induce vasoconstriction in the fingers and skin, but in the muscles of the forearm and leg the reverse is true.

The perennial arguments concerning the etiology and treatment of Raynaud's disease are still not completely settled. With the exception of the Mayo Clinic, most investigators are agreed that preganglionic sympathectomy is distinctly more effective than postganglionic denervation. A reason for this is the lesser degree of sensitization to sym-

pathomimetic substances which results (see above). Lewis<sup>30</sup> states that he is "prepared to accept clinical evidence for this conclusion. The preganglionic operation has the merit not only of producing, so it would seem, the greater vasodilatation, but in avoiding the disfigurement of Horner's syndrome." Lewis adds that, even after this improved operation, he can still induce attacks of Raynaud's disease on direct exposure to cold and that the local abnormality remains. In another article Lewis<sup>31</sup> compares the pathologic changes in the arteries of warm-handed people with those in patients with Raynaud's disease. Intimal thickening becomes distinct in both groups with advancing age and is no greater in the mild cases of Raynaud's disease than in the normal controls. This fits in with Lewis' theory of local increased sensitivity to cold. In the more advanced cases with trophic changes in the skin there is intimal hyperplasia, the arterial lumen being greatly reduced or actually occluded by proliferative tissue and organized thrombus. Opposed to Lewis' theory of an entirely local vascular fault are the findings of Day and Klingman.<sup>32</sup> They studied vasomotor reactions in a 6½-year-old girl with acrocyanosis and found that during sleep there was spontaneous warming and reddening of the hands and feet. Local cooling of the hand during sleep did not cause vasospasm. They believe that their study supports the theory of a central rather than a local origin of this abnormal vasomotor tone.

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relapsing to the severe degree which we have seen occur in some of the ganglionectomies. The absence of the Horner syndrome is also a distinct advantage, though many of the ganglionectomies have lost this syndrome after a few years, again suggesting regeneration of nerve fibers."

In addition to the possibility of late relapse from regeneration, there are other less valid objections to the present methods of preganglionic denervation of the upper extremity. Kuntz, Alexander, and Furcolo,<sup>36</sup> as well as Heinbecker and Bishop,<sup>37</sup> claim that there are both vasomotor and sudomotor fibers in the first thoracic root, so that vasoconstrictor impulses can still reach the brachial plexus unless the white communicating ramus of this nerve is severed. All these observations were made on cats, and one must remember that there are wide anatomical species differences. Hinsey<sup>23</sup> has been unable to find evidence of such fibers in the first thoracic root of animals, and there is certainly nothing to suggest their presence in the large series of postoperative cases that has been examined for this very point at the Massachusetts General Hospital. Objection has been raised by Fatherree and Allen<sup>38</sup> to the physiologic concept that sympathectomized blood vessels become abnormally sensitized to adrenaline and with greater intensity after postganglionic than after preganglionic denervation (Cannon's Law of Denervation). In their experiments these investigators used such large doses of adrenaline that they missed the selective effect which is produced by this hormone on all denervated smooth muscle and with greatest intensity after degeneration of the postganglionic fibers.

A new method of dealing with thrombophlebitis has been advocated and received much favorable support during the past two years. In 1934 Leriche and Kunlin<sup>39</sup> suggested immediate infiltration of the lumbar ganglia with procaine in patients with acute thrombophlebitis, and in a second article Leriche<sup>40</sup> has recommended the resection of these structures in patients with painful swelling, coldness, and ulceration of the legs in the chronic stages. The rationale of the procedure, according to Leriche, depends on the relief of reflex vasospasm, which in turn is responsible for many of the manifestations. DeBakey, who worked with Leriche, brought the method to this country and with Ochsner<sup>41</sup> has written a number of enthusiastic reports about it. They believe that the edema is due to anoxia from reduced circulation and the resultant increase in capillary permeability, and that a series of procaine injections is usually sufficient to interrupt the vasoconstrictor reflex from the thrombosed veins and thereby to increase local circulation, relieve pain, and promote resorption of edema fluid. By preventing the persistence of edema, subsequent fibrosis and the development of chronic lymphedema may be prevented.

*Hyperhidrosis.*—A most interesting and valuable study on sweat secretion in man has been published by List and Peet. They classify sweating as of thermoregulatory, emotional, gustatory (produced by

eating spicy food and confined to the face), spinal reflex, and drug origins.<sup>42</sup> Innervation of the sweat glands is described and the regional loss of thermoregulatory sweating illustrated after various surgical and pathologic lesions of the sympathetic pathways.<sup>43</sup> Two other articles deal with sweat secretion after various drugs<sup>44</sup> and the peculiar disturbances which may occur in the face.<sup>45</sup> An article by White<sup>46</sup> describes the nervous variety of sweating in the hands and feet which is closely related to Raynaud's disease and the satisfactory results after sympathectomy.

*Hypertension.*—The literature on hypertension during the century which has followed the observations of Bright has been reviewed in a provocative manner by Scott.<sup>47</sup> He concludes that all the evidence for the etiology of this condition points to the view that essential hypertension, in the light of Goldblatt's experimental work, is of renal origin. The knowledge that this form of hypertension is of chemical origin and not due to excessive vasoconstriction at first glance does not seem favorable to any neurosurgical form of intervention. Undoubtedly surgical treatment is still in the experimental stage, but opinion is beginning to crystallize that extensive interruption of vasoconstrictor impulses to the splanchnic bed and lower extremities is of value in suitably selected cases. Over three-quarters of the patients show a striking symptomatic improvement, regardless of whether the blood pressure falls or not, and the operation carries extremely little risk. Sympathectomy should be performed on more patients in the early stages of hypertension; it is useless in the severer grades, as well as in the majority of patients over 50 years of age. It is quite obvious that, even if patients are selected with the utmost care, the results are not consistently good and that the fall in the diastolic pressure is not as great as in the systolic. The results of resection of the splanchnic nerves and a limited number of sympathetic ganglia in carefully selected cases with adequate postoperative observation have been summarized in Table I.

TABLE I

AUTHOR	NO. CASES	SIGNIFICANT REDUCTION	MORTALITY	FOLLOW-UP PERIOD
Craig and Adson <sup>48</sup>	237	52%	0	2 mo.+
Moore <sup>49</sup>	22	45%	4.0%	30 mo.+
Smithwick <sup>34</sup>	34	59%	0	1-20 mo.
Braden and Kahn <sup>50</sup>	173	49%	3.4%	*

\*Of 33 cases followed from 2 to 5 years, 30 maintained a satisfactory reduction of blood pressure.

The question has been raised by Volini and Flaxman<sup>51</sup> whether denervation really produces any specific effect on blood pressure. They claim that the degree of symptomatic relief and reduction in blood pressure in the presence of essential hypertension is sometimes greater after nonspecific surgical procedures (hysterectomy, prostatectomy, chole-

cystectomy) than that obtained by extensive sympathectomy. But Page<sup>52</sup> has given valid evidence that the favorable results of sympathectomy are truly specific, pointing out that when the operation is performed in two stages there is only a brief fall in blood pressure after the first stage, but a sudden, far more striking and lasting effect which comes on dramatically as the nerve structures are cut during the second stage. Davis and Barker<sup>53</sup> have found that, in addition to its specific effect on blood pressure, splanchnicectomy may increase the value of potassium sulphocyanate medication.

#### VISCEROMOTOR AND VISCEROSENSORY FUNCTIONS OF THE AUTONOMIC NERVOUS SYSTEM

*Paroxysmal Tachycardia.*—The observation that long-lasting attacks of paroxysmal auricular tachycardia, which cannot be stopped by medical measures and are so severe that cardiac failure threatens, may be stopped by chemical or surgical interruption of the cardiac accelerator nerves is not new, but is not as generally known as the importance of the condition warrants. Coleman and Bennett<sup>54</sup> have reviewed the literature and presented an interesting case report of a patient who had multiple daily bouts of tachycardia coupled with a diseased gall-bladder. In view of two previous fatalities from intractable tachycardia and decompensation in similar cases, they were afraid to remove the gall bladder. By means of an injection of alcohol into the right stellate ganglion (the right seems more important than the left in reducing the irritability of the pacemaking mechanism) the attacks of paroxysmal tachycardia were stopped and cholecystectomy was performed without disturbance of cardiac rhythm four and one-half months thereafter. This was the first period in twenty years during which the patient had been free from her attacks.

A somewhat similar experience has been described by Leibovici, Dinkin, and Wester<sup>55</sup> in which a young man following appendectomy developed a severe form of paroxysmal tachycardia. This proved resistant to medical measures, but ceased abruptly when the stellate ganglion was injected with procaine and did not recur.

*Angina Pectoris.*—Miller<sup>56</sup> has published a small monograph with numerous line drawings which illustrate in a most useful manner the anatomical arrangement of the nerves to the heart. Moore,<sup>57</sup> who has so thoroughly investigated the mechanism of visceral pain, points out that, whereas the somatic system innervates the surface of the body and provides a defense against external violence, the viscera are relatively insensitive to mechanical trauma but develop pain with certain changes in the internal environment. As far as the heart is concerned, the painful stimuli are ischemia and its products (lactic acid).

Three years ago Bérard, one of Leriche's assistants, studied the results of paravertebral alcohol injection in the treatment of angina pectoris in

this country and compared the results with those obtained by other procedures. Of the many different methods which he describes in his thesis,<sup>58</sup> preference is given to stellate ganglionectomy, as performed by Leriche in Strasbourg, and to paravertebral blocking of the upper thoracic ganglia with alcohol. A rather similar study has been reported by Jessen-Aarhus<sup>59</sup> and preference given to the injection method. Flothow,<sup>60</sup> one of the proponents of paravertebral injection, has submitted a number of younger patients without evidence of advanced coronary disease to resection of the inferior cervical and upper thoracic sympathetic ganglia through an anterior incision. This method is also being used at the Massachusetts General Hospital. It gives a higher percentage of relief than removal of the stellate (cervicothoracic) ganglion alone or alcohol injection and also avoids the not too infrequent complication of alcoholic neuritis. In addition, the anterior approach permits the operation to be carried out with the patient lying on his back. Operations in the presence of coronary disease are less safely performed with the patient in the prone position, where interference with respiration and venous return may be dangerous factors.

Raney<sup>61</sup> has advocated a new operation which involves excision of the posterior portion of the third, fourth, and fifth ribs in the prone position. He recommends dividing the lower end of the sympathetic chain and cutting the rami of its second to fifth ganglia, without resection of the ganglia themselves. Although good results are recorded in eleven cases, many theoretical points are open to criticism. From the anatomic angle it is probable that important connections will be missed, at least in some patients, if the fibers through the first thoracic ganglion are not interrupted. It is claimed that the operation is primarily on the efferent fibers to the heart and that it is preganglionic. Whether the first point, that the sensory mechanism is left largely intact, is true or not, the second is incorrect, since the thoracic cardiac nerves contain postganglionic fibers (Nonidez<sup>62</sup>). Raney himself admits that according to the best available evidence the sympathetic fibers are coronary dilator, but he feels that somehow in coronary disease the mechanism may be reversed. Surgeons who have had a wide experience with operations on the upper thoracic sympathetic structures must realize their extraordinary tendency to regenerate unless wide areas are excised.

*Congenital Megacolon.*—The safety and other advantages of procedures aimed at sympathetic denervation of the colon in children with Hirschsprung's disease have become so generally recognized that the older methods of colonic resection are falling into disrepute. Mortality in the latter group is formidably high and, as de Takats and Biggs<sup>63</sup> point out, a progressive dilatation of the segment proximal to the resection has been reported too often to be ignored. The diagnostic and therapeutic value of spinal anesthesia has been re-emphasized by Telford

eystectomy) than that obtained by extensive sympathectomy. But Page<sup>52</sup> has given valid evidence that the favorable results of sympathectomy are truly specific, pointing out that when the operation is performed in two stages there is only a brief fall in blood pressure after the first stage, but a sudden, far more striking and lasting effect which comes on dramatically as the nerve structures are cut during the second stage. Davis and Barker<sup>53</sup> have found that, in addition to its specific effect on blood pressure, splanchnicectomy may increase the value of potassium sulphocyanate medication.

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ing afferent pathways, but by reducing spasm of the internal sphincter. They report an interesting series of patients suffering from dysuria secondary to various forms of chronic cystitis with the predominating feature of vesical spasm, where resection of the superior hypogastric plexus was followed by uniformly good results. In a very similar series of eleven cases Scott and Schroeder<sup>71</sup> have observed striking relief in all but one patient. They believe that better results can be obtained if the upper sacral sympathetic ganglia are resected along with the superior hypogastric plexus, which is contrary to the opinion of Nesbit and McLellan. In patients in whom operation has given insufficient relief, Scott and Schroeder have supplemented the resection by subarachnoid alcohol injection. White<sup>72</sup> has devised a modification of intrathecal alcohol injection which blocks the lower sacral sensory roots bilaterally and has found that this is sufficient to relieve the pain of malignant disease in the bladder neck. This is a most useful method to relieve severe pain in the lower rectum, urethra, perineum, and external genitals, but it entails a considerable risk of bladder paralysis and can therefore be used with safety only in patients who are already on constant drainage. Corollary to this, Simmons<sup>73</sup> has pointed out that the retention of urine, which frequently follows perineal resection of the rectum, is brought about by injury to the parasympathetic fibers which run in the anterior divisions of the lower sacral nerves (*nervi erigentes*). He claims that resection of the superior hypogastric plexus at the time of the preliminary laparotomy and colostomy has been followed by a considerable diminution in the incidence of postoperative retention of urine. This latter point is still open to discussion (Munro<sup>69</sup>).

*Uterine Pain.*—Whereas bladder sensation is in large part, if not altogether, carried in the sacral parasympathetic rami, there is no longer any question that the pain of idiopathic dysmenorrhea is relieved by presacral neurectomy. The cases must be carefully selected to exclude pain from the ovaries and other related structures and the dissection of the presacral plexus must be meticulous and complete. A good anatomical description of this plexus has been given by Labate,<sup>74</sup> based on dissection of seventy-five cadavers, which should be of considerable help to the surgeon who wishes to familiarize himself with this operation.

A most instructive report on the value of presacral neurectomy in essential dysmenorrhea has been given by Meigs.<sup>75</sup> He is the one surgeon who has published statistics in a series of patients where the superior hypogastric plexus was resected without any other pelvic surgery being done to beloud the issue. Of his 20 patients, 15 had a successful result. There were partial successes in 2 other cases and in 3 there were complete failures. Meigs concludes that this operation, with the necessary correction of obvious pelvic abnormalities, is the best form of treatment for patients with true primary dysmenorrhea.

and Simmons.<sup>64</sup> There is also evidence that acetylcholine is of value as a diagnostic test, due to its stimulant action on the parasympathetic outflow (de Takats<sup>65</sup>).

As regards indications for denervation in patients with megacolon, Telford<sup>66</sup> believes that operation should be performed in children who are not relieved by conservative medical treatment by the age of 5 or 6 years. He thinks that bilateral resection of the lumbar chains is the operation of choice. Resection of the inferior mesenteric and superior hypogastric plexuses may be followed by regeneration, and division of the splanchnic fibers is of value only when the ascending colon is involved.

A monograph devoted to the subject of megacolon has been written by Pässler<sup>67</sup> from the University Clinic in Leipzig. This book is a valuable contribution because of its wide review of the literature, theories of etiology, and review of surgical treatment. Pässler points out that there is little to recommend in the older types of operation on the colon and describes the three standard types of neurosurgical intervention. These consist in bilateral removal of the lumbar chains, resection of the inferior mesenteric and superior hypogastric plexuses, and subphrenic splanchnicectomy combined with upper lumbar ganglionectomy. Each of these three procedures has given good results, but the second is preferable when the bladder is enlarged as well as the colon. Pässler describes the different varieties of the condition, its medical and surgical treatment, and the frequent association of enlargement of the bladder with the idiopathic congenital form of the disease. Experiences in 10 cases are reported in detail and the results of sympathetomy in 117 patients summarized from the literature. Of these, 38 were fully relieved, 64 were improved, 12 were not relieved, and 3 died.

*Bladder Pain and Retention.*—The problem of how large a role is played by the sympathetic division in bladder pain and disorders of micturition still remains a subject of dispute. According to the best experimental evidence, bladder sensation and motor power are mediated by the parasympathetic fibers in the second, third, and fourth sacral nerves, although some contractile innervation may reach the region of the trigone and internal sphincter via the sympathetic fibers in the superior hypogastric plexus. This work has been reviewed in McLellan's monograph on *The Neurogenic Bladder*.<sup>68</sup> A comparison of cystometrograms made before and after presacral neurectomy shows that neither the response of the normal bladder musculature to stretch nor its sensation is in any way altered by presacral neurectomy (Munro<sup>69</sup>). Nevertheless, numerous case reports continue to emanate from well-known clinics recording relief from both bladder retention and pain by this operation. According to Nesbit and McLellan,<sup>70</sup> it is possible that sympathetomy may relieve certain forms of bladder pain, not by interrupt-

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*Phantom Limb Pain and Minor Causalgias.*—One of the most puzzling aspects of an already difficult problem is the relation of the sympathetic nervous system to pain in the extremities. The work of Moore<sup>57</sup> has demonstrated conclusively that pain from the arteries of the extremities is transmitted over the mixed peripheral nerves and not over autonomic pathways. The situation in the periphery is quite different from visceral artery pain, where sensory axones which traverse the sympathetic trunks play a most important part. Notwithstanding this apparent elimination of the sympathetic system from the role of sensory innervation of the limbs, a number of convincing reports have appeared in recent years which give evidence that certain types of pain can be relieved by chemical or surgical interruption of the sympathetic fibers. Whether this effect is secondary to an improvement in circulation or to some other obscure cause at present cannot be stated. Two most interesting papers on phantom limb and on post-traumatic pain syndromes by Livingston<sup>76, 77</sup> have recently appeared. In each of these it is brought out that interruption of the reflex arc, either at the trigger point or proximally in the afferent path or in the paravertebral outflow of the sympathetic rami, will often break the vicious circle and yield satisfactory relief. After repeated injections of procaine, and sometimes even after a single block, many of these patients, who are such a problem to the insurance company and the physician, have been cured without the need of a surgical operation.

The purpose of this review has been to summarize new work of fundamental value in understanding the complex integration of the autonomic nervous system in man and reports of clinical cases which emphasize the correctness or fallacy of its surgical application. No new operative procedures of importance have been developed in the past two years. A number of special monographs of considerable value have been published and are listed above.<sup>6, 7, 27, 56, 58, 67, 68</sup> In addition, Scupham, de Takats, and co-workers<sup>78</sup> have written a special article on vascular diseases which gives a very complete summary of this subject. Because of language difficulties it has been impossible to cover the literature beyond the American, English, French, and German sources. Few references from German periodicals have been included, because they have contained little of value.

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# Review of Recent Meetings

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## REVIEW OF THE MEETING OF THE AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS, AND ABDOMINAL SURGEONS, SEPT. 26, 27, AND 28, 1940, EXCELSIOR SPRINGS, MO.

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School of Medicine)*

THE fifty-third annual meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons was held at The Elms, Excelsior Springs, Mo., Sept. 26, 27, and 28, 1940. The meeting was well attended by fellows of the society and their invited guests. The entire program of sixteen papers was presented.

Calvin R. Hannah, Dallas, Tex.: *Home Delivery Service by Students.*—An outline of the obstetrical curriculum at Baylor University was presented. Certain practical considerations of pregnancy for teaching were given; namely, the custom of referring to the fetus in all stages of pregnancy as "the baby" and the importance of recognizing the stages of labor, with attention to the effacement of and dilatation of the cervix. The course and progress of the senior students in home delivery work was outlined. The senior work includes training in the city and county hospitals where students follow the course of labor, do rectal examinations and scrub up for the delivery before the home delivery. Then there is a period of time as "second-call man" when home delivery is observed and assistant work is done preceding the actual delivery. Following this period, the senior does home deliveries and has full equipment. Hannah presented a review of results in a large series of home delivery cases.

George W. Kosmak, New York City, stated that institutional births are increasing in number. It is questionable if this is always ideal, since some institutions are not always so safe. He considers home delivery an essential factor in teaching obstetrics. Grandison D. Royston, St. Louis, discussed hospital facilities for teaching students and home delivery methods. He then demonstrated a portable delivery table and paper drapes, designed by Dr. E. F. Bruning and used on the outpatient service at Washington University. Irving W. Potter, Buffalo, N. Y., outlined his experience with home delivery. He stressed the importance of recognition of labor. James L. Raycraft, Cleveland, Ohio, considered outpatient work a matter for adequate and close supervision. This he stated, is important for good teaching and for good results. Ward F. Seeley, Detroit, urged supervision on home delivery service to avoid repetition of mistakes a student might make. He believes that a minimum amount of equipment is best for the student to use. Hannah, in closing, mentioned the ease with which chloroform

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# Editorial

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## Cooperative Research and Priority

**I**N SUCH strenuous times as now confront us, it is of the greatest importance that information valuable in the care of those in the armed services be made readily available. Investigators, as a group, are rightly slow in publishing their findings until they are sure, beyond a reasonable doubt, of the significance of the data they have obtained. On the other hand, some investigators imagine themselves impelled to hasten publication because they feel that if they wait until completion of their studies someone working in a similar field may establish priority. Publications in the latter category have resulted too frequently in the premature adoption of therapeutic procedures which additional evidence and thought proves to be worthless and at times even harmful.

Several years ago President Conant, in a report to the Trustees of the Harvard Corporation, stated that it was not at all unlikely that the greatest advances in science in the future would come from cooperative research. One might, without fear of contradiction, add to this statement that all significant contributions to medicine have been in a sense the result of nonintegrated cooperative research. Every investigator utilizes, to some degree, the work of others in the conduct of his individual research.

Within the coming months it will become necessary, with increasing frequency, to obtain authoritative information in the shortest possible time. This, in many instances, will require the pooling of our scientific resources. This will be especially true in medicine, where the application of observations made in our laboratories of fundamental science will be put to the test of final clinical verification. It is of the greatest importance that in this program priority play no part and that individual or departmental ambitions be submerged for the greater good.

The investigations already begun in numerous laboratories under the general direction of governmental agencies will demonstrate perhaps the fullest possible effect of cooperative effort. It will show perhaps that a broader fundamental knowledge of a specific subject can be obtained in a shorter period of time by cooperative effort. It may prove to be costly from the economic point of view, but cost in dollars will mean little if the information received will lead to a reduction in the morbidity and mortality of a host of conditions that may confront us.

In such a program of free cooperative effort individual priority, of course, must be submerged. This, I believe, will be of little importance, for after all, while priority in a truly fundamental problem may be of importance, it should be a matter of little consequence, especially at this time, in the daily routine of laboratory and clinical investigation.

—*I. S. Ravdin, M.D.*  
Philadelphia, Pa.

Frederick H. Falls, Vincent E. Freda, and Harold H. Cohen, Chicago: **A Skin Reaction for the Diagnosis of Pregnancy.**—A difficulty in various tests for pregnancy is the obtaining of a suitable antigen. Most precipitation tests for pregnancy are inaccurate due to lack of a high enough percentage of correct results. In looking about for a suitable antigen breast tissue was used and then colostrum. The techniques of injection and control were described. Drawings were presented to show the various reactions. The results in 265 cases of known pregnancy were reported. A series of known controls, including men, children, and gynecologic patients, was reported. A group of problem cases was listed as to accuracy of results.

Lawrence M. Randall, Rochester, Minn., mentioned the common pregnancy tests available. In many of the tests an incidence of error may reach 20 to 25 per cent. This, he stated, is due to the fact that the substances that give a positive reaction are associated with pregnancy, but still may be present in other conditions. In any skin test the correct interpretation of the reaction depends on the wheal formation and one's familiarity with it. A. J. Rongy, New York City, gave examples of misleading reactions in pregnancy tests. Falls, in closing, mentioned biologic reactions that are not 100 per cent accurate, but have stood the test of time and are useful.

Quitman U. Newell, St. Louis: **Transmigration of the Human Ovum.**—Results of studies by the author were cited. Two pregnancies resulting from transmigration of the ovum were reported in a patient who had had the right ovary and left tube removed. The possible explanation of the process of transmigration of the ovum was given.

Fred L. Adair, Chicago, discussed external and internal transmigrations of the ovum. By way of proof of external transmigration, he mentioned the occurrence of ectopic pregnancy on the opposite side from the ovary of recent ovulation, pregnancy in the opposite side of the bicornuate uterus and after operation for the removal of the opposite organs. The subject is of interest because of its association with the problem of fertilization. He included a consideration of the function of the cilia and fimbria of the tube as well as the muscular action of the tube and ovary. In these cases he feels that there is a synchronization of the activity of the organs with endocrinal activity. Joe V. Meigs, Boston, reported another case of transmigration. James L. Raycraft, Cleveland, reported transmigration after plastic surgery on the remaining opposite tube and ovary. A. J. Rongy, New York City, mentioned some points in such a case. David Hadden, Oakland, Calif., outlined possibilities of pregnancy following errors in surgery. George M. Shipton, Pittsfield, Mass., also gave examples of pregnancy after surgical procedures.

C. O. McCormick, Indianapolis, Ind.: **Effects of Obstetrical Anesthesia on the Newborn Infant.**—Apnea is the one common ill effect of the various forms of modern obstetrical analgesia, except those of local infiltration. This frequently observed effect is perhaps largely responsible for the belief that analgesia routinely jeopardizes the infant. The reports of Schreiber and of Cole have done much to foster such an attitude of apprehension. Recent studies, particularly those of Kotz, demonstrate that the methods of relief in obstetrics of paraldehyde administration and the Gwathmey method have more favorable effect on the newborn. Comparisons of initial weight loss, recovery of birth weight, and temperature curve of newborn infants where various methods of analgesia had been used in the mother were demonstrated. Several charts were shown to illustrate the comparative results.

may be used. The preparation on the home service is the same as in the hospital. One student prepares the patient and may do the work of a nurse. Complicated cases are brought into the hospital.

**B. Z. Cashman and John S. Frank, Pittsburgh:** Deep Cauterization of the Cervix—A Factor in Reducing the Mortality of Hysterectomy.—Since infection is an important factor in the mortality of hysterectomy and since there is infection in the cervix in the majority of patients requiring hysterectomy, the authors feel that special procedures are necessary to sterilize the cervix. The infection is frequently so deep-seated that usual cleansing of the vagina and cervix does not reach the infection. The deep cauterization has been the most successful method of sterilizing the cervix and prevents future trouble with the cervical stump. Deep cauterization of the cervix, combined with subtotal hysterectomy, makes total hysterectomy for benign conditions unnecessary. The authors reviewed a series of consecutive hysterectomies by this method for the past six years, presenting tables of results.

Walter T. Dannreuther, New York City, mentioned little difference in mortality of total hysterectomy and subtotal hysterectomy if done correctly. He favors the supravaginal hysterectomy with retention of the cervix, unless the condition of the cervix is pathologic enough to require removal. He mentioned various methods of treatment of the cervix before operation. Virgil S. Counseller, Rochester, Minn., stated that good results depend on working with a method to which one becomes accustomed. He favors total hysterectomy because of the associated reconstruction of the vaginal vault. The results are better after removal of the cervix, especially in multiparas. He quoted a mortality rate of less than 1 per cent in benign conditions with total hysterectomy. Frank presented some tables and figures that were not included in the paper as read. Joe V. Meigs, Boston, cited several cases of carcinoma of the cervix after subtotal hysterectomy. He mentioned his own observations of such cases and expressed his favor of the total hysterectomy. A. J. Rongy, New York City, stated that no single method of hysterectomy is good in all cases. He described how he favors the peritonealization of the cervical stump and draws it up to prevent vaginal shortening. William H. Weir, Cleveland, stated his preference for the complete hysterectomy. He also mentioned a number of cases illustrating his points. A. D. Campbell, Montreal, Canada, presented some points important in the reduction of mortality in hysterectomy. He believes it important to take blood sugar determinations before operation. The technique of operation should be determined by the limitations of the operator. Drainage should be established by an opening in the vaginal vault below the peritoneum. Total hysterectomy carries the lower mortality. Channing Barrett, Chicago, presented a number of points in the technique of hysterectomy. James W. Kennedy, Philadelphia, considered cauterization of the cervix important before hysterectomy. He uses soldering irons in his technique. He mentioned that possibly 95 per cent of all hysterectomies throughout the country are supravaginal. Mortimer W. Hyams, New York City, classified various degrees of cervical involvement with infection. Conditions of treatment differ with different degrees of cervical involvement. In deep involvement the effects of cauterization and conization differ. He doubts if deep areas are reached in fourth degree involvement. Cashman, in closing, pointed out that subsequent stricture is not a factor in deep cauterization if hysterectomy is done. No further treatment of the cervix is necessary if deep cauterization is well done.

Good results have been obtained by the use of these solutions in the work outlined by the authors. Examples of usefulness in long labors, and in retraction ring cases were given.

H. B. Van Wyck, Toronto, Canada, considered various procedures that may be carried out to prevent shock in labor. E. L. Cornell, Chicago, stressed various factors in the prevention of shock. James E. Davis, Ann Arbor, Mich., advised that the problem of shock often was a matter of distribution of blood mass in the body of the patient. Pride, in closing, mentioned the quantity of the solutions that might be necessary to give the desired effect in acidosis and alkalosis.

Clifford B. Lull, Philadelphia (by invitation): **Pubertas Praecox Due to Ovarian Tumors.**—The author expressed his purpose in the essay to call attention to the fact that ovarian tumors are the causative factor in precocious puberty. He reported in this paper what he believes to be the youngest patient ever operated upon for a granulosa cell tumor of the ovary with immediate reversion to normal infantile tendency. The second case he reported was of a follicular cyst of the ovary at 20 months of age, with definite signs of puberty. This patient also returned to normal following operation. Photographs of the patients and histologic sections were shown.

James E. Davis, Ann Arbor, Mich., mentioned the unusual fact of a presentation of two cases in patients of early age, with unusual sex development. He discussed phases presented in these two cases. Davis pointed out the life periods of granulosa cell activity; namely, (1) to the age of puberty, with precocious sex development; (2) period of fertility, with 85 per cent of cases showing abnormal bleeding and many with hyperfemininity; (3) postmenopausal period, with psychic changes and signs of sex rejuvenation. Malignancy seems to be present in 25 to 30 per cent of granulosa-cell tumors. These tumors show many histologic differences and various stages of development. H. M. N. Wynne, Minneapolis, discussed the presentation and mentioned points in a case. Due to the small number of these tumors, he suggested a national register where they might be recorded. Joe V. Meigs, Boston, mentioned the problem as not a common one. He told of the difficulty in differentiating between types. Both types have granulosa cells and theca cells. Precocious puberty is also associated with hypothalamus tumors, as in Albright's syndrome with brown spots, bone cysts, and precocious puberty. Frank R. Smith, New York City, discussed the effect of x-ray therapy in treatment of granulosa cell tumors. The results in general are bad. Lull, in closing, stated there was no uterine enlargement in either of these cases, and no brown spots on patients.

E. L. Cornell, Chicago: **Objections to Induction of Labor in Normal Pregnant Women.**—The discussion was limited to normal pregnant women. He mentioned the complications that may arise from induction, and a résumé of 200 consecutive cases in private practice was given. Particular attention was paid to the size of the baby in the cases, from seven days before term until thirty days after the date of term. The conclusion reached was that it is seldom justifiable to induce labor in a normal pregnant woman.

John H. Moore, Grand Forks, N. D., illustrated cases of induction with some unsatisfactory results, such as excessive bleeding and delayed labor after ruptured membranes. He advised against assuming responsibility of induction for the sake of convenience. Buford G. Hamilton, Kansas City, Mo., cited cases of induction of labor with early rupture of the membranes and failure of labor to follow soon. He stated that the hazards are too great unless a definite indication

**Emmett D. Colvin**, Atlanta, Ga., discussed the importance of evaluation of all factors where drugs were used for obstetrical analgesia. He urged that one keep in mind the possible influence of drugs on the uterus to produce inertia. With many analgesics operative delivery becomes necessary; hence the possibility of more birth injuries. Colvin presented a series of cases where nembutal and paraldehyde were used for analgesia. He reviewed the results in this series, considering success of amnesia, results with length of labors, type of deliveries, apnea in infant, and behavior of infant after delivery. **William Wayne Babcock**, Philadelphia, remarked on the possibility of central nervous system changes in the child after analgesia. **Ward F. Seeley**, Detroit, spoke of the possible brain changes of a permanent nature in the newborn child. These so-called "devastation areas" in the brain may result without primary mortality. He expressed the opinion that initial weight loss was of little importance in this observation. **Grandison D. Royston**, St. Louis, indicated that most apnea of the newborn was the result of delay in delivery. Opines do depress the respiration. He cited satisfactory results in the use of hyoscine and barbiturates. **Fred L. Adair**, Chicago, stated that the barbiturates do depress the respiration in the newborn. Delay in establishment of respiration is of great importance. **George W. Kosmak**, New York City, spoke in particular of some aspects of analgesia and possible effect on the newborn. Closing remarks by **McCormick**, covered the points of discussion.

**A. J. Rongy and A. B. Tamis**, New York City: **The Palatal Arch and the Pelvis; a Preliminary Report.**—The authors considered the female pelvis, its shape and form. Does it conform to general body configuration? Do the bony cavities have a definite relationship characteristic of the individual? Does the formation of the palatal arch give us a clue to the type and kind of a pelvis a woman may have? The paper, based on a study made of the palatal arch in 74 patients, was the attempt of the authors to answer the above questions. The various measurements of the palate were carefully made and the capacity studied. The kind and type of labor were accurately recorded in this series of cases. The changes in the oral mucosa during early pregnancy were also observed. Factors indicating easy or difficult labor were tabulated.

**J. C. Litzenberg**, Minneapolis, Minn., stated that everything about the pelvis is still unknown. One is unable to prove any definite relationship between the palatine arch and the pelvis. Configuration of various parts of the body depends on the constitutional development of the patient. **Ralph E. Campbell**, Madison, Wis., discussed the development of the skull in relation to the endocrinological development of the patient.

**W. T. Pride**, Memphis, Tenn.: **Acidosis and Alkalosis in Gynecology and Obstetrics.**—Following studies of urine in cases of long labor in which evidence of acidosis was plain, studies of the blood  $\text{CO}_2$  were made in labor. A series was obtained of the  $\text{CO}_2$  of the blood at the end of the first, second, and third stages of labor. Following the obtaining of accurate data by blood studies of patients in labor, methods were considered whereby the correction of the degree of acidosis or alkalosis as indicated by  $\text{CO}_2$  determinations might be brought out. Experimental studies were made on dogs to determine the strength of lactic acid solution, and the strength of soda bicarbonate solution that could be given safely intravenously. After it was determined that a 1 per cent lactic acid solution could be used, and that a 2 per cent soda bicarbonate solution could be used, it was then determined to a quantitative degree just how much of either solution was necessary to alter the  $\text{CO}_2$  combining power of the blood to the normal range level.

distance from the ovarian surface were measured micrometrically. It was shown that in the early stages of follicular growth up to a diameter of 0.25 mm., there is a descent of the follicles from the albuginea toward the hilus and that there is an ascent of the larger follicles back toward the surface. This ascensus begins with the appearance of the theca layers. Examination of the theca layers shows that the growth is an eccentric one. There is a one-sided thickness of the theca interna toward the ovarian surface. This forms a wedge-like theca interna cone with a triangular cut surface which always points to the nearest part of the ovarian surface. This infiltrating growth plows a path for the follicle through the stroma and albuginea. The granulosa layer frequently adopts the shape of the theca cone. In all mammalian species the theca cones grow divergently toward the ovarian surface, except in the horse ovary, where the theca cones grow convergently toward the only free spot, the "ovulatory pit." To demonstrate the theca cone which is present only in actually growing follicles, it is necessary to cut serial sections which are cut perpendicularly to the ovarian surface.

Stuart B. Blakely, Binghamton, N. Y.: *The Psychology of Pregnancy.*—The author compared male and female psychology. The desire for a baby is basic in woman's nature and cannot be successfully denied. Causes of the mental state of pregnant women, responses of the psyche to pregnancy, prominent in the early months, are changes in disposition, cravings or aversions, and nausea and vomiting. Included in the essay are other changes which the author deals with as psychic, including sexual personality, emotions of resentment and anger and anxieties and fears. He considered the pregnant woman's attitude toward abortion, abortifacients, and abortionists. The attitude of the laity toward obstetrics and the obstetrician was discussed. Finally, dreams in pregnancy as well as the esthetics of pregnancy and mental hygiene of pregnancy were covered.

I. W. Potter, Buffalo, N. Y., stated that physiologic changes of pregnancy cause a number of disturbances of pregnancy and must be considered inciting factors. R. T. La Vake, Minneapolis, stressed the importance of understanding as well as possible the psychology of pregnancy. He discussed the attitudes toward abortion and stated that he does not feel that scruples toward abortion are on the wane. Blakely, in closing, considered nausea and vomiting of pregnancy to be largely psychic. He also states that he believes induced abortions are extremely common.

E. Lee Dorsett, St. Louis: *Reoperation Analysis of 125 Gynecologic Cases.*—The unsatisfactory results following gynecologic operations were discussed. Some of these poor results were found to be due to the formation of postoperative adhesions that caused partial intestinal obstruction, and from which patients suffered almost constant pain. The author feels that some of the unsatisfactory results with the formation of adhesions were due to improper time selected for performing an operation on certain cases of inflammatory disease; operating upon cases of salpingo-oophoritis in the acute stages; the rough handling of tissues; too conservative measures in certain cases of chronic pelvic inflammatory disease; the failure to cover properly all raw surfaces following operative procedures; the improper use of drains; the failure to select the proper type of operation to cope with the situation at hand; the habit of using routine procedures and trying to make one operation fit every case. All these factors and many more are reasons why some of our unsatisfactory results follow gynecologic operations. One hundred and twenty-five cases were presented. The essayist was the original operator in a certain percentage of cases; the remainder had been operated on by other men. Some of these cases had two, three, and four laparotomies.

is present. George W. Kosmak, New York City, spoke of the number of papers presented for publication on the subject, "Induction of Labor." Albert W. Holman, Portland, Ore., presented a series of 1,163 cases of induced labor with figures on fetal and maternal mortality. Herman B. Van Wyck, Toronto, Canada, contributed to the discussion on the propriety of induction of labor. A. B. Rongy, New York City, indicated his ideas on the problem of a patient's being overdue and stated that induction of labor was never indicated for the sake of convenience. George F. Pendleton, Kansas City, Mo., spoke of induction and its features of responsibility involved. Irving W. Potter, Buffalo, N. Y., spoke of his attitude toward induction. He considered the process of effacement of the lower uterine segment. Cornell, in closing, again called attention to the normal cases only included in his essay.

**Ralph E. Campbell, Madison, Wis.: The Repair of a Series of Complete Tears of the Sphincter Ani With Extension up the Posterior Vaginal Wall by the Warren Vaginal Flap Operation.**—The author presented the steps in the vaginal flap technique for repair of complete laceration of the pelvic floor. The operation differs from the original Warren technique. Success of the operation depends on good blood supply, careful pre- and postoperative treatment, and not too much tension on suture lines. The operative technique was illustrated by lantern slides. Particular attention was given to preparation of the vaginal flap, the repair of vaginal wall above the flap, the closure of the levators, the closure of the sphincter and anal mucosa, and the skin closure. The method of removal of the remainder of the flap was described. Postoperative treatment was outlined. A series of 39 cases was presented with 95 per cent satisfactory results in 37 out of 39 cases.

**Wm. F. Mengert, Iowa City, Ia.,** pointed out the advantage of the flap operation in eliminating raw areas in the rectal wall. He also considered the results with mobilizing and drawing down the rectal wall to eliminate raw areas in the rectal wall. He reviewed the results in eleven cases treated in this manner. **Fred L. Adair, Chicago,** spoke of the results as presented being mostly in older women. He stated that the best time to make such repairs is at the time of delivery. **Channing W. Barrett, Chicago,** noted that complete lacerations should be repaired at delivery. He also stated that in most cases the rectal wall could be mobilized and brought down.

**James R. McCord, Atlanta, Ga.: President's Address.**—McCord spoke on a subject to which he has always devoted much time and thought, that of maternal mortality in the Southern states. He showed the high maternal mortality both in white and negro women. A series of 97 maternal deaths in colored obstetrical patients was presented. By careful analysis he divided the series into those that were preventable and those nonpreventable. Of the preventable deaths he listed those in which the possibility of prevention rested with the patient and those in which the physician was at fault. He also listed the deaths in the series from nonobstetric causes. It was well shown by him that negro women in the South are had obstetric risks. Closely related to the problem of maternal mortality is the economic situation in the South. The speaker gave a most enlightening résumé of the economic situation in the Southern states.

**Erwin O. Strassmann, Houston, Texas: The Theca Cone and Its Tropism Toward the Ovarian Surface, a Typical Feature of Human and Mammalian Follicles. Thesis Awarded the Foundation Prize.**—This paper is a summary of microscopic research done from 1921 to 1939. The findings presented are based on 18,000 microscopic sections of ovaries in four mammalian orders: primates, carnivora, rodentia and ungulates. The diameter of human growing follicles and their

Herbert E. Schmitz, Chicago, in discussing the cases, presented the picture of nationalities in Chicago. He compared the incidence of carcinoma in the various nationalities and races found there. He also included in his discussion a consideration of the effect of radiation on vaginal tract bacteriology.

C. O. McCormick, Indianapolis, Ind., presented motion pictures of *The Use of Rectal Ether Anesthesia*.

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## THE TWENTY-THIRD ANNUAL MEETING OF THE AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION

PAUL HOLINGER, M.D., CHICAGO, ILL.

THE twenty-third annual Meeting of the American Broncho-Esophagological Association was held June 5, 1940, at the Waldorf-Astoria Hotel, New York City. Lyman Richards, Boston, presided.

In his presidential address Richards traced the development of broncho-esophagology, and the relation of this development to the training of new men in the specialty. He stressed the importance of the mastery of technique of peroral endoscopy which was first developed by otolaryngologists who devoted only a portion of their time to endoscopy. However, the necessity of constant practice and the advantage in experience gained through specialization in this work have led him to believe that in the future more men will devote their entire time to this field. Opposed to this, mention was made of the high degree of skepticism which still exists in the minds of certain internists and surgeons, in spite of the tremendous increase in both the diagnostic and therapeutic phases of broncho-esophagology. On the other hand, Richards justified the position of other internists and surgeons who have invaded the field of peroral endoscopy because of their intimate knowledge of problems dealing with thoracic pathology.

New instruments were presented by the following members of the association:

Simon Jesberg, Los Angeles, presented a series of esophagoscopes which combined the sled type tip of the Haslinger esophagoscope with distal lighting. He also presented miniature 3 and 4 mm. infant bronchoscopes as well as a protecting mask and interchangeable lenses for glasses which can be used in endoscopic work.

Sam Roberts, Kansas City, Mo., presented a bronchoscopic biopsy forceps similar to laryngeal cup forceps, lengthened for bronchoscopy use.

Arthur Penta, Schenectady, N. Y., presented a pair of electrically heated glasses to be used in endoscopic work. The heating coil of wire, fused into the glass, prevents the lens from fogging.

Several case reports were presented:

Ernest M. Seydell, Wichita, Kan., demonstrated roentgen films of a 14-month-old infant who had had symptoms of an esophageal foreign body. The roentgen films showed a disklike object, which, on anteroposterior projection, appeared to be located in the cervical esophagus. Negative esophagoscopy examination led to further studies and the disk was proved to be a center of ossification of the sternum. The presentation was discussed by T. E. Carmody, Denver, L. H. Clerf, Philadelphia, C. E. Pitkin, Cleveland, and others who reported having had similar experiences.

**F. Smead**, Toledo, Ohio, stated the unsatisfactory situation of having to operate on a patient a second time. He stressed the careful selection of patients for operation, the careful handling of the parts, the production of no raw surfaces. In removing the appendix one should be particularly careful. Following gynecologic surgery endometriosis is frequently the cause of reoperation. **William H. Vogt**, St. Louis, considered the matter of preoperative preparation. With the use of more local anesthesia, more careful handling of the tissues results. **Adam P. Leighton**, Portland, Me., reported some experiences of operative results in postoperative cases. **George W. Kosmak**, New York City, advised the more extensive use of the transverse abdominal incision, as well as the reduction of traction to a minimum. **Dorsett**, in closing, mentioned the part played by endometriosis in reoperation of cases. He also spoke of the importance of wound-closure methods as a part of important operative procedures.

**David Hadden**, Oakland, Calif.: **Clinical Experience With Testicular Extracts in Obstetrics and Gynecology.**—The essayist stated that our present knowledge justifies a report upon the use of an extract, the mention of which, a few years ago, would have subjected one to criticism. This report was also a word of appreciation of one, who, the author states, would have gone far in endocrinology if his life had been spared. The anatomical and physiological reasons that seemed to justify the preparation and the use of such an extract in gynecology were briefly given. The factors that led to its experimental use in the vomiting of pregnancy and the satisfactory results are considered. Its wider application in such conditions as menorrhagia and acne came as a result of failure with more supposedly orthodox preparations. The author described the preparation of the extract as devised by Moore and Archibald.

**W. A. Coventry**, Duluth, Minn.: **Actinomyces of the Ovary.**—The author reported one case of actinomyces of the ovary with case history, operative findings, surgical pathology, and subsequent course of the patient to date. He reviewed the cases of actinomyces in Duluth hospitals. There were three cases in one hospital and four in another. Of the seven cases, three involved the glands of the neck. In three cases the patients are still living. Three cases involved the intestinal tract; all are dead. The one case of actinomyces of the ovary is still living. In the literature there are less than 100 cases reported. The author gave a brief review of the literature. A great question in the cases in general is the primary source of infection.

**Frederick H. Falls**, Chicago, showed the predominance of right-sided involvement in actinomyces of the ovary. This may extend to the opposite side after the first operation. He described the type of growth of the organism. He also considered recurrent cases after operation and reported his recent experiences in such a case. **Lewis F. Smead**, Toledo, Ohio, reported his experience in a recent case. **George F. Pendleton**, Kansas City, Mo., brought up questions concerning the subject.

**Frank R. Smith**, New York City: **Nativity and Carcinoma of the Cervix.**—This paper covered a statistical study of the nationality incidence of cervix carcinoma at Memorial Hospital. The patients with carcinoma of the cervix were compared as to nationality with the patients presenting other types of lesions and with a cross section of the gynecologic clinic. A discussion of the reasons for the findings was included, although these reasons are theoretical rather than statistically proved.

Gordon Berry, Worcester, Mass., and C. A. Heatly, Rochester, N. Y. Other cases of surgical relief of cardiospasm were presented by the discussors who all stressed the exhaustion of conservative methods of relief before resorting to surgery. Uniformly good results were reported with the use of the method described by Heatly. Unsuccessful results followed other surgical measures.

Millard F. Arbuckle, St. Louis: **Bronchoscopic Treatment of Lung Abscess.**—Reference was made to the published opinions of numerous thoracic surgeons regarding their methods of treatment of patients with lung abscesses. Arbuckle stated that the importance of bronchoscopy was seldom stressed. He pointed out that the role of bronchoscopy in the treatment of lung abscess was in establishing endobronchial drainage through removal of granulation tissue which is often found between the main bronchus and the abscess, and directing an aspirator to aspirate the contents of the abscess itself. Of 43 cases in Arbuckle's series of acute, subacute, and chronic lung abscesses, whose duration varied between two weeks and three and one-half years, 19 recovered completely and 4 showed satisfactory improvement on bronchoscopic aspiration; whereas, 20 failed to recover or improve on bronchoscopic aspiration alone. The ages of the patients ranged between 3½ and 65 years. Arbuckle stressed the use of extra length aspirating tips, the removal of granulation tissue plugs which had been visualized by lipiodol, and the control of hemorrhage through the use of cocaine and adrenalin. Arbuckle also stressed the necessity of a thorough preliminary examination to establish the location of the cavity before bronchoscopy. C. L. Jackson, Philadelphia, in discussion, stressed the fact that one should not consider bronchoscopy versus surgery in the treatment of lung abscess, but that the two specialties should work in close harmony with one another in the management of this pulmonary disease. Porter Vinson, Richmond, Va., described the insufflation of powdered sulfanilamide into the infected lung as a means of treatment, stating that it had been frequently used prior to further surgical procedures in a number of cases of lung abscess. Arbuckle closed the discussion by mentioning that avertin had been used throughout as an anesthetic and that there had been no fatalities during or following any of the bronchoscopic procedures.

Samuel Pearlman, Chicago: **Sarco-carcinoma of the Esophagus. Is There Such an Entity?**—Pearlman analyzed 17 cases reported in the literature and 8 additional cases of his own of so-called carcinosarcoma of the esophagus. He illustrated the anaplastic nature of certain of the squamous-cell carcinomas in which the boundaries between carcinomatous and sarcomatous elements were indistinct. He concluded that in his cases the pathology was that of a primary carcinoma of the esophagus associated with an inflammatory process which had compressed the epithelial cells to give them a spindle shape. The manner in which the cells were cut likewise influenced the appearance of the specimen as seen through the microscope. For these reasons Pearlman felt that the so-called sarco-carcinoma was a questionable entity.

Chevalier L. Jackson and George S. McReynolds, Philadelphia (by invitation): **Anesthesia for Peroral Endoscopy.**—The authors, through a study of questionnaires, reviewed the current practice in anesthesia for direct laryngoscopy, bronchoscopy, esophagoscopy and gastroscopy throughout the country and described the methods of anesthesia now in use in the Department of Broncho-Esophagology at Temple University. The purpose of their study was to consider the safety and efficiency of the various anesthetics now in use and to determine, if possible, the anesthetic which would cause the least discomfort to the patient both

Louis H. Clerf, Philadelphia, reported a case of a tuberculous periesophageal abscess which had produced stenosis of the esophagus. The roentgen findings had revealed a marked esophageal stenosis suggestive of an esophageal neoplasm. Esophagoscopy examination demonstrated a swelling of the posterior wall of the esophagus which was topped by a yellowish pustule. When opened, 30 c.c. of pus were drained in which many tubercle bacilli were found. There was no demonstrable evidence of tuberculosis elsewhere and the patient made an uneventful recovery. A year later an esophagoscopy examination showed the esophagus to be normal. The process was considered to be due to the erosion of a tuberculous lymph node into the esophageal wall.

Leroy A. Schall and Louis Johnson, Boston (by invitation), reported the case of a 5-month-old infant who had had respiratory difficulty dating from birth. A bronchoscopic examination revealed a tracheal compression at the carina, and, since the child obtained relief from the dyspnea while the bronchoscope was in place, a tracheotomy tube was inserted. The infant died because of a profuse hemorrhage and the autopsy revealed a double aortic arch, the right and left arches constricting the trachea. The paper was discussed by Paul Holinger, Chicago, A. E. Hammond, Detroit, and C. L. Jackson, Philadelphia, who reported similar cases of tracheal and bronchial compression due to cardiovascular anomalies.

George O. Cummings, Portland, Me., described the treatment of a traumatic tracheal atresia by means of graduated core molds. The patient had received a crushing injury to the trachea in an automobile accident, destroying both airway and voice and necessitating a tracheotomy. A tracheal occlusion developed which was demonstrable on roentgen films. The trachea was opened under general anesthesia, and through the use of core molds the tracheal lumen was re-established. Chevalier Jackson, Philadelphia, stressed the importance of starting treatment early in these cases.

Porter Vinson and W. E. Pembleton, Richmond, Va. (by invitation), presented the case of a patient 63 years of age who was having repeated severe pulmonary hemorrhages. Bronchoscopic examination revealed a mass in the right bronchus which was removed and proved to be a hilar lymph node with tiny areas of calcification. The microscopic examination of tissues taken from the bronchial wall at the point of ulceration showed tuberculosis. The bronchial lumen was re-established by the removal of tissue and the patient made a complete recovery.

The following papers were read:

Clyde A. Heatly, Rochester, N. Y.: *Surgical Management of Intractable Cardiospasm.*—Heatly mentioned the various theories of the etiology of cardiospasm, and described the types of operations which had been suggested and performed for relief of intractable cases. He presented two cases of patients who had not obtained relief in the usual manner following dilatation on whom a surgical anastomosis of the lower end of the esophagus and the cardiac portion of the stomach in the manner of the Finney pyloroplasty had been done. Through a left midline incision the peritoneum had been reflected from the diaphragm and the esophagus. The cardia was drawn down by a tape passed between the cardia and the esophagus, and the lateral anastomosis followed. One of the patients was 79 years of age, the other 24 years. In the first the esophagus remained dilated following the operation, but there was an easy flow of barium into the stomach. The dilatation of the esophagus in the second patient was reduced and there was likewise an easy flow of barium into the stomach. The paper was discussed by Porter Vinson, Richmond, Va., M. F. Arbuckle, St. Louis,

**F. W. Davison, Danville, Pa.: Some Observations on the Control of Humidity and Temperature in the Oxygen Tent.**—Davison made detailed studies of various factors governing the atmospheric conditions in oxygen tents and described the physiologic effect due to the abnormal conditions within the tent. He demonstrated an ingenious way of controlling the humidity within the tent through the use of a special attachment which permitted the inflowing oxygen to be supersaturated with moisture before being introduced into the tent. The moisture is supplied by a mechanical humidifier, thus avoiding the heat ordinarily produced by croup kettles. He described the use of this apparatus for treatment of acute laryngotracheobronchitis and presented the results of cases treated in this manner.

**Herman E. Bozer, Buffalo, N. Y.: Bronchial Collapse Without Clinical Signs of External Pressure.**—Bozer presented three cases of bronchial collapse which appeared to be due to the inability of the cartilaginous framework of the bronchus to maintain the lumen under certain physiologic conditions. In each of the 3 cases the left bronchus was involved and in 2 of the cases an atelectasis was present. In these 2 cases breath sounds could be heard satisfactorily over the involved areas when the bronchoscope was held in place or the bronchus held patent by means of forceps. In the third case relief of the cardinal symptom, dyspnea, was obtained through the use of adrenalin. The collapse in this case, as the author suggested, might have been on the basis of a bronchospasm or a collapse of the bronchus due to the strain which accompanied a severe cough.

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## NORTHERN SURGICAL SOCIETY

JAMES HINDMARSH, STOCKHOLM, SWEDEN

THE twenty-second meeting of the Northern Surgical Society was held in Oslo, Norway, June 29 to July 1, 1939. The president was Professor Emeritus P. Bull; the general secretary, Professor E. Dahl-Iversen.

**Thesis I. Diabetes and Surgery.**—The Discussion was opened by Torben G. Knudtzon, Copenhagen; H. C. Hagedorn, Copenhagen; J. P. Strömbeck, Stockholm; and Per Hanson, Oslo.

T. G. Knudtzon, Copenhagen, reported 635 cases of diabetes among surgical patients who had been treated at the two departments of surgery at the Municipal Hospital in Copenhagen during a twenty-year period from 1919 to 1939. Of these cases, 347, or 55 per cent, were of special types often associated with diabetes, such as gangrene, carbuncle, etc.; while 176 cases, or 28 per cent, were associated with accidental conditions, such as injuries, acute surgical abdominal diseases, etc. The mortality for the whole group was 19 per cent. During the first five-year period, before the introduction of insulin, the mortality was 26 per cent. It fell to approximately 11 per cent during the second five-year period, but rose again to 18 per cent during the last five years.

The mortality of diabetic gangrene was especially high in febrile cases and in patients with severe diabetes. The majority of cases were treated conservatively. The importance of prophylactic measures was emphasized.

In the cases with carbuncle the mortality was highest when the lesion occurred on the back of the neck. The author recommended excision of such carbuncles and treatment to control the diabetes.

as regards the endoscopic procedure and the anesthetic. Eighty-six, or approximately 80 per cent, of the questionnaires sent out were returned. Of these, the majority stated the use of some type of premedication. The principal types used were morphine and atropine or morphine and some type of barbiturate, while only two used morphine and scopolamine. A large majority of the returns indicated that most endoscopists used a general anesthetic for some of the procedures, the indications being the age of the patient, unusual size or shape of a foreign body, or the lack of an operating team. Seventeen of the 86 never used a general anesthetic. Of the local anesthetics used, cocaine, pontocaine, and larocaine were the anesthetics of choice in the order mentioned. The procedure of application of the local anesthetic varied in detail with almost every clinic. The usual procedure was that of a preliminary spray of the pharynx with the topical anesthetic, followed by painting or swabbing the posterior pharyngeal wall and the insertion of sponges on curved sponge carriers into the pyriform sinuses. The method in use at the present time at the Jackson Clinic is that of premedication with morphine and atropine and occasionally a barbiturate. In children no anesthesia is used and in adults the anesthetic is first sprayed into the pharynx and then fractionally instilled onto the larynx and into the trachea with a laryngeal syringe. This procedure is used in adults for the procedures of direct laryngoscopy and bronchoscopy, but for esophagoscopy the pharynx is merely sprayed. In gastroscopy the Schindler anesthetizing tube is passed into the esophagus for the administration of the local anesthetic.

**M. C. Meyerson, New York City: Bronchoscopy in Tuberculous Children.**—Meyerson discussed the findings in 29 children suffering from pulmonary tuberculosis who had been referred for bronchoscopic examination during the year. The indications were those of atelectasis, noisy breathing, the localization of an active lesion, or the removal of secretions for bacteriologic examination when the examination of the stomach contents and feces had been negative in suspicious cases. Thirteen of the 29 patients had positive findings. These differed little from the endoscopic findings of adults with pulmonary tuberculosis. In 7 of the 29 patients an obstruction of the tracheobronchial tree by compression of mediastinal glands was found. Atelectasis was present in 4 of the patients; secretions produced the bronchial obstruction and atelectasis in 3 cases, and granulation tissue in 1 case. In 9 cases tubercle bacilli were recovered from the bronchoscopically removed secretions when the sputum examinations had been negative prior to the bronchoscopy. Meyerson felt that the ulcerogranulomatous lesion is not seen as commonly in children as it is in adults.

**George R. Brighton, New York City: Laryngotracheobronchitis.**—The author mentioned the increasing tendency of designating all cases of laryngeal obstruction in children as due to laryngotracheobronchitis. He limits the diagnosis to those cases requiring surgical relief. Of 27 cases reported, the majority had been observed during the past four years with a death total of 11 cases, or 40 per cent mortality. The average age of the patients was 27 months; the youngest, 11 months. The author felt that sulfanilamide had not influenced the death rate in his series, 6 of the 10 patients receiving sulfanilamide having died. Routine treatment was that of humidified air, oxygen, or oxygen and helium, with tracheotomy the method of choice if operative relief became necessary. The disease was compared to laryngotracheobronchitis in chickens, the disease in chickens having been established as due to a filterable virus. The lymphocytosis and other features of the pathology were both grossly and microscopically similar to those seen in chickens. The author feels, therefore, that laryngotracheobronchitis may be due to a virus.

The proper use of insulin has lowered the mortality from diabetic gangrene and has made possible a more frequent use of conservative therapy. Even so, the end results of diabetic gangrene are not satisfactory. Prophylactic treatment is of great importance. In diabetic patients with infections, carbohydrates and insulin should be given in adequate amounts, foci of infection should be eliminated as early as possible, and proper surgical remedies for infection should be applied.

Per Hanson, Oslo, reviewed his experience, covering the surgical treatment of 55 cases of diabetes which he treated medically during the period 1936 to 1938. He stated that it is important to keep the total calorie intake low, but to give carbohydrates in large quantities. It is preferable to give repeated, small doses of insulin rather than a few large doses. Five of the 55 patients died, but in no instance was the death attributed to the diabetes or to treatment with insulin. Generally, there were remarkably few complications.

Olof Arnell, Stockholm, gave a report concerning the surgical treatment of patients with diabetes, based upon experiences at the Maria Hospital, Stockholm. A series of 1,782 cases of diabetes had been treated during the years 1910 to 1938, and 358 of these had been operated upon, with a mortality of 18.4 per cent. Gangrene was present in about 10 per cent. Acute abdominal diseases often provoked less pain in diabetic patients than would be expected from the severity of the condition. The mortality in cases of appendicitis was very high; and cholecystitis was more liable to be severe and carried a greater risk of perforation than in non-diabetic patients. Absence of sugar from the urine does not always exclude the presence of diabetes. The urinary test for ketones never should be neglected. Before the introduction of insulin the mortality was 10.2 per cent higher than the recent mortality rate. Since the beginning of the use of insulin there have been no deaths from diabetic coma.

Fredrik Therkelsen, Copenhagen, discussed the use of a high carbohydrate diet and insulin in surgical patients with diabetes, and reported 12 cases. Urinary ketones disappeared rapidly and the diabetes was easily kept under control. Acidosis did not occur, and there were no complications due to insulin. The surgical treatment was conservative.

H. Thelander, Stockholm, stated that the use of insulin has increased the number of pregnancies in diabetic females. At the same time it has improved the prognosis so that the mortality is scarcely higher than in nondiabetic women. The internist and obstetrician should collaborate as closely as possible. Cesarean section should not be performed unless the obstetrician considers it to be unavoidable. The infant mortality is still high among diabetic patients, so the condition should be carefully controlled in the child.

Abraham Troell, Stockholm, discussed the problem of diabetes and accidents. Glycosuria may occur after trauma to any part of the body, but it is of no significance. Genuine diabetes may occur following peripheral trauma in patients previously manifesting no symptoms of the disease. According to the author, this fact indicates a relationship between the injury and the diabetes in those cases, even though there may have been an hereditary tendency toward the disease or a latent diabetes. Diabetes tends to delay healing after physical injuries, and therefore warrants compensation for damage.

E. Lundberg, Drottningholm, stated that in cases of pregnancy in diabetic women therapeutic abortion must be performed in the presence of slight indications, unless some contraindication exists. Infant mortality is not much lower today than it was before the introduction of insulin. It is important to maintain the mother's blood sugar level as nearly normal as possible during pregnancy.

Among the abdominal conditions, diseases of the appendix, gall bladder, and pancreas were most important. In appendicitis severe pathologic changes occurred early. In cases of appendical abscess the author advised careful control of the diabetes and, whenever possible, early incision and drainage of the abscess. Cholecystitis was a serious complication among diabetic patients, and the author recommended operation at an early stage in the presence of gallstones or cholecystitis.

For pregnant patients the author advised therapeutic abortion if the diabetes were severe.

In cases of accidental injuries the diabetes frequently became more difficult to control, but usually responded well to proper antidiabetic treatment.

Nitrous oxide anesthesia is preferred for diabetic patients who require surgical treatment for some associated condition. Spinal anesthesia is satisfactory in certain cases, but ether and chloroform should be avoided.

Operations were performed upon 387 of the patients (61 per cent). Although the risk has been reduced by the use of insulin, severe surgical procedures should be carried out upon diabetic patients only if the indications are positive. Among such patients, arteriosclerosis and myocardial damage frequently occur at an early age. Pneumonia, sepsis, and arteriosclerosis were the most frequent contributory causes of death. The author stated that in the future the mortality from sepsis might be reduced, but he expected an increase in the number of deaths from arteriosclerosis and probably no change in the mortality rate from pneumonia.

H. C. Hagedorn, Copenhagen, pointed out that, since the introduction of insulin, the prospects for patients suffering from diabetes associated with surgical complications are almost as good as for patients free from diabetes. The development of surgery and the accommodations of modern hospitals have contributed to the favorable results. The characteristic progress of the complications is not, as one may believe, due to the high percentage of grape sugar present in the tissues, but it is probably caused by a change in the cellular metabolism which reduces the amount of carbohydrate and fat in the tissues so that the conditions are far from normal. The rapid effect of insulin on obstinate wounds supports this assumption. Another factor may be the accumulation of normal or abnormal metabolic products. Injury to the nerves and vessels constitutes another important point, and consideration of the problem from this angle might throw some light on the unusual progress of many complications in diabetic patients.

The author called attention to similarities between diabetes and other endocrine diseases, such as myxedema and Addison's disease. He advised proceeding cautiously in the treatment of diabetic gangrene, especially if the patient's general condition is improving.

J. P. Strömbeck, Stockholm, stated that the increased duration of life resulting from the introduction of the use of insulin has added to the number of diabetic patients coming for surgical treatment. Cases of diabetic gangrene have been increased.

Narcosis and other conditions associated with an operation disturb the carbohydrate metabolism more in diabetic than in nondiabetic patients, but the administration of carbohydrate and insulin reduces the risk to such an extent that it is almost the same in both instances. Dehydration and chloride deficiencies must be eliminated. The author expressed a preference for nitrous oxide and ether anesthesia, and he stated that chloroform, avertin, and evipan were to be avoided. Insulin should be given to all diabetic patients coming for surgical treatment, and may be given by continuous intravenous drop infusion if necessary. Excessive amounts of insulin, leading to hypoglycemia, carbohydrate deficiency, and hepatic insufficiency, are especially dangerous.

The proper use of insulin has lowered the mortality from diabetic gangrene and has made possible a more frequent use of conservative therapy. Even so, the end results of diabetic gangrene are not satisfactory. Prophylactic treatment is of great importance. In diabetic patients with infections, carbohydrates and insulin should be given in adequate amounts, foci of infection should be eliminated as early as possible, and proper surgical remedies for infection should be applied.

Per Hanson, Oslo, reviewed his experience, covering the surgical treatment of 55 cases of diabetes which he treated medically during the period 1936 to 1938. He stated that it is important to keep the total caloric intake low, but to give carbohydrates in large quantities. It is preferable to give repeated, small doses of insulin rather than a few large doses. Five of the 55 patients died, but in no instance was the death attributed to the diabetes or to treatment with insulin. Generally, there were remarkably few complications.

Olof Arnell, Stockholm, gave a report concerning the surgical treatment of patients with diabetes, based upon experiences at the Maria Hospital, Stockholm. A series of 1,782 cases of diabetes had been treated during the years 1910 to 1938, and 358 of these had been operated upon, with a mortality of 18.4 per cent. Gangrene was present in about 10 per cent. Acute abdominal diseases often provoked less pain in diabetic patients than would be expected from the severity of the condition. The mortality in cases of appendicitis was very high; and cholecystitis was more liable to be severe and carried a greater risk of perforation than in non-diabetic patients. Absence of sugar from the urine does not always exclude the presence of diabetes. The urinary test for ketones never should be neglected. Before the introduction of insulin the mortality was 10.2 per cent higher than the recent mortality rate. Since the beginning of the use of insulin there have been no deaths from diabetic coma.

Fredrik Therkelsen, Copenhagen, discussed the use of a high carbohydrate diet and insulin in surgical patients with diabetes, and reported 12 cases. Urinary ketones disappeared rapidly and the diabetes was easily kept under control. Acidosis did not occur, and there were no complications due to insulin. The surgical treatment was conservative.

H. Thelander, Stockholm, stated that the use of insulin has increased the number of pregnancies in diabetic females. At the same time it has improved the prognosis so that the mortality is scarcely higher than in nondiabetic women. The internist and obstetrician should collaborate as closely as possible. Cesarean section should not be performed unless the obstetrician considers it to be unavoidable. The infant mortality is still high among diabetic patients, so the condition should be carefully controlled in the child.

Abraham Troell, Stockholm, discussed the problem of diabetes and accidents. Glycosuria may occur after trauma to any part of the body, but it is of no significance. Genuine diabetes may occur following peripheral trauma in patients previously manifesting no symptoms of the disease. According to the author, this fact indicates a relationship between the injury and the diabetes in those cases, even though there may have been an hereditary tendency toward the disease or a latent diabetes. Diabetes tends to delay healing after physical injuries, and therefore warrants compensation for damage.

E. Lundberg, Drottningholm, stated that in cases of pregnancy in diabetic women therapeutic abortion must be performed in the presence of slight indications, unless some contraindication exists. Infant mortality is not much lower today than it was before the introduction of insulin. It is important to maintain the mother's blood sugar level as nearly normal as possible during pregnancy.

**J. Tillgren**, Stockholm, stated that in cases of acute surgical diseases associated with diabetes, an extra dose of insulin should be administered previous to the operation, even if the patient is unable to take food. Mild cases of diabetes should be allowed a diet without insulin as soon as possible after the operation. Full diet is not advocated and, even in children, it must be considered an excess.

**Uno Carlborg**, Stockholm, reported his experiences with oscillometric examinations in 123 cases of diabetes. Of this group of patients, 34 per cent manifested pathologic oscillograms in the leg. Gangrene was present in 10 patients (all with pathologic oscillograms), and 36 patients had subjective and objective symptoms in the form of pain, sensation of cold, etc.

**Abraham Troell**, Stockholm, expressed the opinion that the operative mortality in patients with diabetes would be reduced if larger doses of insulin were given prior to operation. He advised the administration of 10 to 20 units of insulin, and the injection of glucose solutions subcutaneously and by rectum, two or three doses being given in a day.

**Esben Kirk**, Copenhagen, stressed the importance of the test for bicarbonate in the plasma in cases which are approaching or are actually in coma. The intravenous injection of an isotonic solution of sodium bicarbonate relieves acidosis without danger of alkalosis during the interval before the effects of insulin can be produced.

**R. Romanus**, Hälsingborg, discussed a series of 700 cases of diabetes treated during the years 1925 to 1937. Among these, there were 62 cases of gangrene. Only 26 patients were operated upon. The diet consisted of large amounts of fat and moderate amounts of carbohydrate.

**A. Tallroth**, Göteborg, recommended evipan for anesthesia in diabetic patients.

**F. Saltzman**, Helsingfors, discussed a series of 514 cases of diabetes treated at the Maria Hospital in Helsingfors during the period 1930 to 1939. Ten per cent of the cases had required surgical operation.

**Johns Ipsen**, Sönderborg, stated that in diabetic gangrene the temperature of the skin of the affected foot does not differ from that of the unaffected foot. This indicates that the gangrene is not due to a deficiency of blood supply and explains the favorable results obtained by conservative treatment in cases which are not too far advanced. Gangrene associated with arteriosclerosis requires different therapy.

In conclusion, **Knudtzon** stated that it seemed to be generally accepted that large quantities of carbohydrates should be given together with adequate amounts of insulin, and that acidosis should be prevented, or, if present, combated. **Strömbeck** warned against the use of an increased dose of insulin before operation in patients with well-controlled diabetes. **Hanson** emphasized that the caloric intake should be low under all circumstances and that carbohydrates should be given by mouth or by rectum. Only in cases of emergency should carbohydrates be given subcutaneously or intravenously.

**Gunnar Nystrom**, Borgå, reported 4 cases of malignant tumor of the kidney in children and discussed the pathologic anatomy and treatment of embryonal tumors. He stated that hematuria occurs in only about 10 per cent of such cases. The prognosis is worse than in cases of Grawitz tumors, the percentage of cures being not over 10 per cent at best. Three of the author's 4 patients died. The fourth was still alive a few months after operation. The author assumed that the tumors originate from the mesenchyma. In the discussion, **Borch-Johnsen**, Oslo, reported 1 patient still living eight and one-half years after operation, which had been performed at the age of 16 months.

Frans Sorensen, Copenhagen, summarized data based upon the observation of 250 cases of fibroadenomatosis of the breast. In more than 100 cases, treated partly with and partly without estrin, and in which histologic examinations had been made, it was found that the therapeutic effect of estrin was proportional to the amount of pathologic hyperplastic interlobular connective tissue. Examination after periods of one to four years revealed that one-third of the patients treated with estrin were subjectively and objectively free from symptoms. Malignant changes did not occur in any case.

John Hellstrom, Stockholm, related experiences with the operative treatment of diverticula of the urinary bladder. Since 1933 the author has operated upon 10 such cases: 9 males and 1 female. There was 1 postoperative death from coronary sclerosis. In 8 cases radical operation was performed by invagination of the diverticulum with the aid of Pean's forceps or by suction, after the bladder had been opened. In 2 cases one of the ureters opened into the diverticulum. In 1 of these a collar was left around the ureteral orifice, and this was sutured into the vesical defect resulting from extirpation of the diverticulum. In the other case a stone was present in the dilated ureter. Ureterolithotomy was performed and an anastomosis was established between the ureter and the diverticulum.

G. Levander, Köping, stated that he had operated upon 2 patients with good results. He advised an extravesical approach after having tamponed the diverticulum from within the bladder.

N. Backer-Gröndahl, Bergen, discussed the advisability of shortening the period of confinement to bed following operations. If the patient is allowed to be up as early as possible, the danger of thrombosis and embolism is decreased and nursing care is facilitated. The economic advantage is obvious. The author reported 435 patients who had been permitted to be up within 7 days following abdominal operations. Among the group there were 49 cases of gastric resection.

In the discussion, E. Landelius, Gävle, stated that for some time he had been allowing elderly patients to sit up in bed as early as the first or second day following prostatectomy or hernia repair.

G. Bohmansson, Örebro, demonstrated an apparatus which enabled postoperative patients to evacuate their bowels without the aid of an attendant and in a sitting position.

N. Backer-Gröndahl, Bergen, concluded by stating that patients quickly learn not to contract their abdominal muscles. By avoiding the median incision in cases of appendicitis, the period of postoperative confinement to bed may be shortened for these patients.

Gunnar Bauer, Mariestad, reported 11 cases with a renal type of pain, but without other positive urologic findings, in which renal denervation (sympathectomy) produced relief. The pain had been present for months or years. There were no serious complications, and in 1 case there was a decrease of urinary casts after the operation.

James Hindmarsh, Stockholm, discussed the treatment of intussusception in children in a group of 66 cases. Between the years 1930 and 1934, 24 cases had been treated by trying to obtain reduction by the injection of a contrast medium enema under fluoroscopic control. Between 1935 and 1939, 42 cases were treated by immediate operation if the nonoperative reduction failed on the first attempt. The mortality for the entire group, among whom 47 cases were operated upon, was 7.6 per cent. During the first period the mortality was 16.7 per cent and during the later period it was 2.4 per cent. The author concluded that preliminary injection of a contrast enema reduced the risk of operation to a minimum.

Ivar Moene, Bergen, reported a case of von Reeklinghausen's disease associated with ganglioneuroma of the stomach in a 54-year-old man. Roentgen examination revealed a tumor on the lesser curvature which at operation proved to be a ganglioneuroma the size of an orange. The patient is alive and well one and one-half years after operation.

Gunnar Redell, Upsala, discussed the occurrence of ascending infections of the biliary tree following anastomotic operations carried out upon the bile ducts. Reviewing 809 Swedish cases (1914 to 1937), he found that postoperative infections were very uncommon. He emphasized the importance of a large stoma, allowing unimpeded passage through the anastomosis. Anastomosis of the bile ducts carries less risk of infection than anastomosis of the gall bladder.

In the discussion, Ph. Sandblom, Stockholm, stated that in animals cholangitis always follows anastomotic operations. In human beings cholangitis is certain to be present in many cases without producing clinical symptoms and is usually found only at post-mortem examination. One may not draw conclusions, therefore, concerning the frequency of cholangitis merely on the basis of clinical symptoms. In reply, Gunnar Redell expressed the opinion that the results of animal experimentation are not entirely comparable to conditions found in human beings.

John Rø, Oslo, discussed the pathogenesis of pain occurring after cholecystectomy. He stated that 35 per cent of a group of patients complained of persistent pain following cholecystectomy. Most of these manifested a tonic spasmodic condition of the duodenum and an altered reaction to morphine. In normal patients the intraduodenal pressure increases slowly and only moderately after morphine; whereas, in patients with postcholecystectomy pain the drug evokes a rapid, marked increase in pressure associated with typical attacks of pain. The pain may be relieved by the administration of amyl nitrite or nitroglycerin.

Roar Strøm, Drammen, discussed thyreotoxic affections of the liver. His experience included post-mortem examinations of cases of thyreotoxic affections and examinations of rabbits after prolonged administration of thyreotoxin. Liver function tests were applied to patients with hyperthyroidism before and after treatment as well as to healthy control patients. The rabbits were tested in a similar manner, and perfusion tests also were carried out on the surviving liver of rabbits. In the cases examined at necropsy and in the rabbits treated with thyreotoxin, morphologic alterations of the liver were observed. The galactose tolerance test is frequently positive in cases of thyreotoxic affections and the patients present an inclination toward fasting hypereitricemia and an abnormally increased alimentary citricemic load curve. The principal cause of decreased carbohydrate tolerance in cases of thyreotoxemia is an assimilation deficiency of the liver, a condition due to an action of the thyroid substance on the liver epithelium, irrespective of the quantity of glycogen present in the liver or of other morphologic alteration.

**Thesis II. Intracranial Injuries Due to Blunt External Force and the Conditions Produced by Such Accidents.** The discussion was opened by Aarno Snellman, Helsingfors; Haakon Saethre, neurologist, Oslo, and G. Røvig, Oslo.

Aarno Snellman, Helsingfors, reviewed 1,076 cases of skull and brain damage treated during the period 1932 to 1938 at the Red Cross Hospital of Finland in Helsingfors. In this group 275 (25.5 per cent) presented skull injuries. In 80 per cent there was evidence of an organic intracranial lesion, and in 30 per cent the intracranial damage was severe. Spinal puncture was performed in many of the intracranial damage cases, but usually not earlier than forty-eight hours following the trauma. Sub-

arachnoid bleeding was relatively common, even in slight injuries, and it increased in proportion to the violence of the trauma.

Cases with increased intracranial pressure were divided into two classes: (1) acute increase of intracranial pressure with a tendency toward compensation; (2) acute increase of intracranial pressure without a tendency toward compensation. Cases in the latter group included: epidural hematoma (7 cases), subdural hematoma (9 cases), combination of epidural and subdural hematomas (3 cases), and blockage (8 cases).

The symptomatology of increased intracranial pressure may be grouped according to three different types: (1) a symptom-free interval, delayed primary unconsciousness, and syndrome of acutely increasing pressure; (2) primary unconsciousness, a symptom-free interval, and secondary unconsciousness, etc.; (3) primary incessant unconsciousness.

The duration of the patients' stay at the hospital should be individualized. In this group patients without skull fracture usually stayed 8 to 24 days, while patients with fracture stayed 15 to 33 days.

Among the 27 patients showing increased intracranial pressure, 20 were operated upon, of whom 16 died. Twenty per cent were saved. The author believed that one-third of such cases might be saved by operation if the conditions were favorable. Chronic subdural hematoma should be evacuated subtemporally and the sac should be washed out.

The total mortality was 5.8 per cent (63 cases). Twelve patients (1.1 per cent) died of meningitis. The cases of meningitis were all associated with skull fracture. More than 50 per cent of the fatal cases died within twenty-four hours and about 80 per cent within three days. In order to improve the results of treatment, each case should be controlled carefully and the latest attainments of brain surgery should be available.

Haakon Saethre, Oslo, stated that certain individuals exhibit increased susceptibility to trauma. Among 316 cases, 13 (5 per cent) had had more than one head injury. Thirty per cent of the acute head injuries showed evidence of alcoholism, and in 122 cases of traumatic psychosis there were 44 cases of chronic alcoholism.

Comotio cerebri is defined as a clinical syndrome resulting from injury to the trunk of the brain (Bernier). In cases of increased intracranial pressure edema plays a more important role than does hemorrhage. Among 258 cases of acute injuries, 62 per cent exhibited signs of this syndrome, but only 30.6 per cent of these were pure commotio syndrome. In the late material commotio syndrome was present in 71.6 per cent of 331 cases. Thirty-five per cent of the late material and 54.7 per cent of the acute cases exhibited neurologic suppression symptoms. In the acute cases nystagmus and other eye symptoms were predominant. In the cases with delayed symptoms otologic disturbances were most common. In 8 per cent of the late material disturbances of the olfactory and gustatory organs were present. Severe dementia was present in 3 cases. Traumatic epilepsy occurred in 5 per cent of the cases.

Meningoencephalopathy due to trauma should be diagnosed only on the basis of positive objective findings, such as neurologic symptoms, pathologic findings in the cerebrospinal fluid, or abnormal pneumogram.

The term "traumatic cerebral general syndrome" (Förster) is adequate for designating the subjective symptoms and should be distinguished from the term "post-traumatic neurosis," the latter being applied to cases without skull trauma. Patients with head injuries, however, may exhibit purely nervous symptoms.

The neuropsychologic symptoms in cases of trauma should be grouped as follows: (1) primary symptoms (primary conditioned psychoreflex, etc.); (2) secondary symptoms (associated with reactive hypochondria, querulousness, depression, etc.).

The author recommended centralization of observations, treatment, and evaluation of injury, especially in cases of patients with insurance.

Gunnar Rövig, Oslo, reported a series of 90 cases of head injuries in which pain persisted for long or short periods after the accident. All patients had undergone neurologic, ophthalmologic, acoustic-vestibular, and encephalographic examinations as well as measurements of spinal fluid pressure and chemical examination of the spinal fluid. Only patients who had been perfectly well before the accident were included. The majority of the patients complained of headache, vertigo, and psychic and vegetative disturbances. Tinnitus and ophthalmic or otologic disturbances were common. Eleven patients had epileptiform attacks. Objective examination revealed:

Psychic symptoms	55 cases
Cranial nerve disturbances	74 cases
Motor disturbances	14 cases
Disturbances of co-ordination	12 cases
Sensory disturbances	9 cases
Abnormal reflexes	58 cases
Ophthalmic disturbances and disturbances of eye muscles	51 cases
Acoustic-vestibular disturbances	26 cases
Pathologic cerebrospinal fluid (including increased pressure)	45 cases
Clinical intracranial lesions	18 cases
Positive encephalographic findings	20 cases
Aggravation or simulation symptoms	8 cases

The author emphasized the value of the encephalogram as an objective method of studying conditions after the injury. In making an interpretation of the findings, the results of the other examinations should be taken into consideration in order to arrive at a rational evaluation of craniocerebral damage.

S. A. Brofeldt, Helsingfors, related experiences with the treatment of skull fractures at the Red Cross Hospital of Finland. Among 1,076 cases with head injuries, there were 275 cases of skull fracture. Fifty-three of these died of brain injury, including 12 cases with meningitis. Five cases with meningitis survived. Fractures which communicated with the sinuses were treated by operation (trepanation and drainage of the sinus) if the skin was broken or if the anterior or posterior wall of the sinus was splintered. Cases with compound fracture of the skull involving the ear were treated conservatively unless an otitis developed. In cases with meningitis operation was performed.

J. Cedermark, Stockholm, reported upon a series of 1,960 cases with head injuries which had been treated at the Maria Hospital during the years 1920 to 1936. Among these, 153 patients had died during their hospital stay and 179 had died later. The cause of death in the latter group usually was not related to the injury. Autopsies had been performed in 109 cases. In the group of patients who had died in the hospital, death was due to the skull injury alone in 124 cases, while in 29 cases there were other severe injuries associated with the skull injury. Eighty per cent of the fatal cases died within forty-eight hours after the accident. The remaining 20 per cent died later from meningitis or pneumonia. The importance of conservative treatment in cases of fracture of the base of the skull in order to avoid meningitis was emphasized. In follow-up studies, 1,450 patients were re-examined, and approximately one-third of the entire group complained of persisting disturbances (one-half of the cases with skull fracture and one-fourth of the cases without fracture). Among 148 insured patients who complained of persistent disturbances, 27 per cent were judged to be entitled to compensation; 39

per cent of the insured patients and 36.7 per cent of the noninsured patients complained of disturbances.

Paul Fjeldborg, Vejle, reviewed observations made upon 287 patients with injuries of the skull in whom spinal puncture had been performed and who had been followed for one or two years after completion of the treatment. Among the patients who had been unconscious for one hour or less, there was blood in the spinal fluid in 144 and no blood in 117 cases; 46.5 per cent of the patients without blood and 54.7 per cent of those with blood in the spinal fluid were free from symptoms at the follow-up examinations. Only 4 of the 26 patients who had been unconscious for more than an hour showed no blood in the spinal fluid. Two of these, or 50 per cent, presented no late symptoms. In the 22 cases without blood in the spinal fluid, 36.4 per cent were free from late symptoms. Fjeldborg concluded that the presence or absence of blood in the spinal fluid was without prognostic value.

Otto Mikkelsen and Fredrik Therkelsen, Copenhagen, reported a series of 211 cases with head injuries and the results of follow-up examinations in 200 patients who had been treated at the Commune Hospital in Copenhagen during the period 1932 to 1934. Of the group of 211 patients at the time of admission, 163 had been considered to be uncomplicated cases of commotio cerebri, but subsequent studies revealed that only 58 per cent were "pure" cases; whereas, the others presented fracture of the skull, blood in the spinal fluid, and neurologic symptoms. Among the 200 patients who had been followed, 34 per cent complained of persistent headache and/or vertigo. Among 161 patients who had resumed work, 47 (29 per cent) complained of persistent headache or vertigo; 53 per cent of the patients manifested more or less severe disturbances after dismissal from the hospital.

Mogens Fog and Axel Lund, Copenhagen, discussed neurologic symptoms associated with acute trauma of the skull and stated that intracranial lesions were found often in patients who had been suspected of having only commotio cerebri. Sequelae were grouped into four classes: (1) chronic commotio syndrome (a morbid state due to organic damage; encephalograms or ventriculograms sometimes reveal abnormalities); (2) post-traumatic neurosis; (3) traumatic encephalopathy; and (4) post-traumatic epilepsy without other clinical indications of organic brain damage.

Björn Kristensen, Copenhagen, reported a series of 191 cases with fractures of the skull, treated at the Hospital in Sundby. There were 35 deaths. Death occurred within twelve hours in about 50 per cent and within forty-eight hours in 75 per cent of the fatal cases. The average period of hospitalization was three weeks. Examinations after two to five years revealed that 49 patients were free from symptoms, 12 manifested impaired working capacity, and 9 patients were judged to have 8 to 25 per cent disability.

Sigurd With, Copenhagen, stated that the treatment of uncomplicated commotio cerebri should be individualized. He reported a series of 394 cases treated at the Hospital in Sundby during the period 1924 to 1934. The patients were confined to bed only until the subjective symptoms had disappeared. In most cases (257) this was less than a week. Subsequently 16.1 per cent of the patients presented persistent complaints, but in most of the cases they were mild. There is no evidence to indicate a correlation between the intensity of the acute symptoms and the persistence of disturbances. The previous existence of neurosis is apparently not important. Sixty-six per cent of the patients returned to work within one month and 84 per cent were able to work within three months.

Einar Schie, Drammen, discussed the use of spinal puncture in cases of skull trauma. For two years all cases of skull injury had been treated by spinal puncture, intravenous injection of hypertonic glucose solution, and limitation of fluid intake. The results were better than in corresponding groups of patients treated by hypertonic glucose injection or bed rest alone.

In the discussion Kristian Kristiansen, Oslo, reported that neurologic examination of 209 patients with skull trauma revealed neurologic suppression symptoms in 67 per cent. Some of the symptoms disappear some days or weeks after the accident, indicating that they are caused by slight hemorrhages. Most frequently suppression symptoms are referable to the third, fourth, or sixth cranial nerve, but they may originate from the fifth, seventh, eighth, or ninth nerve. Treatment should be conservative. The injection of 25 per cent  $MgSO_4$  is important. The total mortality was 5 per cent. Only 5.1 per cent of the cases were operated upon. The principal indication for surgical intervention is progressive unconsciousness. The operation is performed by removing a small portion of the skull subtemporally. Patients with severe brain injury and accelerated pulse should not be operated upon, because they do not survive operation. In patients with epidural hematoma operation should be performed as soon as possible, but in patients with subdural hematoma a period of observation should precede operation. Patients with skull fracture should rest in bed for at least three weeks.

M. Eirto, Helsingfors, stated that, among 540 cases studied at the Red Cross Hospital of Finland, primary unconsciousness was present in 90.4 per cent; 54.7 per cent exhibited amnesia with regard to the accident; 24.8 per cent exhibited alterations of the patellar reflex; and the Babinski sign was positive in 8.7 per cent. Respiration was irregular in 5.5 per cent, and 3 per cent of the cases exhibited Cheyne-Stokes type of breathing.

Marti Hämäläinen, Kuopio, called attention to the principles of physics in relation to traumatology. The important factor is kinetic energy, which is proportional to one-half of the product of mass times the square of the velocity.

H. Olivecrona, Stockholm, stated that trepanation should be performed upon the slightest suspicion of extra- or subdural hematoma. Openings should be made on both sides, over the anterior and posterior branches of the middle meningeal artery. He opposed desiccation therapy. The period of bed rest should not be too short, and subsequently the patient should be kept under strict control. Persistent symptoms are usually due to organic changes. Injuries in the region of the diencephalon cause especially prolonged disturbances. Such cases frequently have a lowered metabolic rate and often respond favorably to thyroid medication.

J. Hellstrom, Stockholm, discussed the difficulty of excluding the presence of extradural hematoma. He reported a patient who had been operated upon because he had developed unconsciousness after a symptom-free interval. No hematoma was found, but the patient died from fat embolism.

R. Ingebritzen, Oslo, approved the use of the term "traumatic neurosis" in patients with skull injuries. In some patients with a latent neurosis the trauma may operate to produce a symptomatic neurosis. He disagreed with Berner's assumption that hemorrhage into the fourth ventricle is the only cause of unconsciousness and death. Such hemorrhages may be found associated with other conditions, such as poisoning, and are not found in young animals killed by a blow on the head.

K. A. Lagergren, Hasselholm, reported 2 cases of *pneumococcus meningitis* which had developed after fracture of the skull and which had been successfully treated with a special compound pneumococcus serum.

H. Saethre, Oslo, disapproved of the use of the term "chronic commotio syndrome." Late symptoms are mostly organic and the symptom complex should be termed "traumatic cerebral general symptoms." The term "traumatic neurosis" is justified on condition that skull fracture is associated with other injuries.

P. Bull, Oslo, stated that observations on the large material collected and reported confirmed the fact that many symptoms which formerly had been considered to be due to aggravation and simulation really have an anatomic basis.

E. Landelius, Gävle, described a technique for spinal puncture which consisted of inserting the needle about 0.5 to 1 cm. to the right of the median line and advancing it in a medial and slightly cranial direction. He stated that this method decreased the risk of inserting the needle too far and that there were fewer failures than with median puncture.

H. Olivecrona, Stockholm, discussed the surgical treatment of Ménière's disease, and stated that medical treatment is usually unsuccessful. During a ten-year period, 60 cases were operated upon by Dandy's method of intracranial section of the vestibular nerve. There was no mortality, and recurrence of symptoms occurred in only 2 cases.

Einar Perman, Stockholm, discussed problems of military surgery, emphasizing the necessity for development of practical methods. Accommodations suitable for operating rooms should be provided, similar to the "*pavillons opératoires*" of the French army. Apparatus for sterilization should be adequate and should be installed in special cars. All severely wounded patients and those recently operated upon should be attended locally for at least eight days. Immediate transport of such cases increases the mortality.

John Holst, Oslo, discussed the indications for and results of treatment by extrapleural pneumonolysis and extrapleural pneumo-oleothorax: (1) tuberculous process too active to permit thoracoplasty, (2) extensive bilateral tuberculosis, (3) cavities near the hilus (when thoracoplasty gives unsatisfactory results), (4) contraselective pneumothorax.

Forty-six patients were operated upon with an operative mortality of 4.4 per cent; 38 patients were followed for four to twenty-one months. Among these, 28 showed no cavities and 22 (58 per cent) showed no bacilli. This method offers aid to patients who previously would have been placed in the inoperable group.

Gunnar Nystrom, Upsala, reported successful pneumonectomy for removal of a metastatic carcinoma the size of a fist in a woman, aged 61 years, who had been operated upon for cancer of the uterus ten years previously. Preliminary pneumothorax was instituted. The operative procedure was carried out under local anesthesia, supplemented with infusion of 2 c.c. of 10 per cent evipal in saline solution. Oxygen was administered by nasal catheter. Almost the entire seventh rib was resected. The pulmonary hilus was infiltrated with 3 per cent novocain and it was clamped with forceps. A transfixion ligature of catgut was applied, the hilus was cut with the diathermy knife, and the lung was removed. The mucous membrane of the bronchial stump was cauterized with a diathermic ball. The arteries and veins were then individually ligated, and two catgut ligatures were placed on the bronchial stump. The air was aspirated and the thorax was closed. There were no complications.

In the discussion, John Holst, Oslo, reported material covering 31 lobectomies with 4 postoperative deaths, and 6 pneumonectomies with 2 postoperative deaths.

John Holst, Oslo, reported 11 cases of mediastinal tumors and benign peripheral lung tumors which had been operated upon without any mortality. He stated that, if pneumothorax and thoracoscopy cannot be performed because of adhesions, broad lateral thoracotomy should be performed after the removal of one entire rib. Mediastinal tumors should be removed transpleurally except in the case of mediastinal struma. The latter should be removed by upper mediastinotomy after dividing the cartilage of the first, or up to the third, rib.

In the discussion, Axel Odellberg, Östersund, reported 2 cases of intrathoracic tumors, a ganglioneuroma and an echinococcus cyst. Both were operated upon and cured. The echinococcus cyst was removed by simple suction.

A case of mediastinal neurinoma, successfully removed, was reported by R. Ingebritzen, Oslo.

G. Nystrom, Upsala, pointed out that single-stage operations for echinococcus cyst are attended with risk of serious allergic collapse, because the cyst contents may enter the open pleural cavity.

E. Åkerberg, Örebro, discussed the treatment of bleeding ulcers and presented material based upon 140 operations for hemorrhage during the period 1929 to 1938. The mortality was 13 per cent, or twice as high as for operations in a hemorrhage-free interval. Roentgen examinations were carried out during the stage of bleeding in more than 95 per cent of the cases (295 examinations) and caused no damage. Blood transfusion did not exert a hemostatic effect. Follow-up examinations of 168 cases of gastric resection (chiefly Billroth I) in patients who had been operated upon during, or shortly after, the stage of bleeding, revealed that recurrent hemorrhages occurred in almost 20 per cent. It is, therefore, important to study and evaluate the symptoms and to limit the indications for operation.

In the discussion, G. Bohmansson, Örebro, stated that blood transfusion may cause renewed bleeding.

Axel Christensen, Aker, discussed the immediate results of surgical treatment of chronic gastric ulcers. The material included 1,100 cases treated medically during the period 1924 to 1938, and 422 cases treated surgically during the period 1915 to 1939. In the first group there were 19 deaths and in the latter group (434 operations) there were 16 deaths, including 2 from hemorrhage. The author assumed that one-half of the patients treated medically were cured, while the remaining half of the group manifested persistent symptoms indicating necessity for operation. On this basis the mortality in patients treated medically is comparable to that following surgical treatment. The operative mortality is 3.7 to 3.8 per cent and is equally divided between resections and gastroenterostomies. Most of the deaths are due to technical deficiencies. The author's personal cases included 254 patients with 5 deaths, a mortality of less than 2 per cent. Resection is the method of preference (Billroth II). Gastroenterostomy should be performed only in cases of pyloric stenosis and in patients over 50 years of age. The author emphasized the importance of postoperative dietary management and of the use of local anesthesia and routine drainage for twenty-four hours following operation. Since the introduction of the use of routine drainage in 1930, no death from peritonitis has occurred. Follow-up examinations revealed good results in 60 per cent of cases following gastroenterostomy and in 86 per cent following resection.

In the discussion, E. Landelius, Gävle, stated that 638 operations had been performed for ulcer at the hospital in Gävle between the years 1928 and 1937. There had been 47 deaths (7.4 per cent mortality); 110 perforated ulcers had been operated upon, with 16 deaths. Resection (Billroth II or Reichel) had been performed in 415 cases. Resection should be performed in young patients and at an early stage of the disease. The patients should be given a normal mixed diet including vitamins.

N. Backer-Grøndahl, Bergen, described and demonstrated a kidney rest, made of stainless steel, which permitted fixation of the patient's pelvis in any desired oblique position. He recommended it especially for operations performed under spinal anesthesia.

G. Levander, Köping, discussed the relationship of periosteum to bone repair. Periosteum had been implanted subcutaneously in very young rabbits. The cambium layer disintegrated, irrespective of whether it was implanted alone or together with bone tissue. It encouraged bone repair in the same manner as the fully developed bone tissue.

bone tissue. The author assumed that it contained a bone-repairing substance which encouraged the mesenchyma to bone repair. The cambium layer might be correctly qualified by the term, "accretion of the bone tissue of mesenchyma type."

S. Annersten, Upsala, discussed the biochemistry of bone formation. He had used the method of developing heterotopic bone formation by bone extract and assumed that the process was caused by a substance with hormonelike action. This substance is soluble in alcohol and is probably of lipoid nature; it can be isolated by concentration and is not type specific. Chemical studies were carried out with regard to the relation of calcium, carbonic acid, and phosphorus to the callus. The findings suggested certain points which may help to clarify the problem of increasing alkali reserve and of alkaline pH of the tissues of the callus.

Alf Gundersen, La Crosse, Wis., presented data concerning transurethral prostatic resection in 100 patients over 75 years of age. The postoperative mortality was 5 per cent. Follow-up examination of 76 patients revealed satisfactory results in 72 cases. The prostate should be removed by radical operation (four-fifths of the gland); bleeding should be meticulously controlled; and asepsis is of great importance.

In the discussion, Stein F. Holst, Oslo, stated that 403 patients had been treated for disturbances of the prostate at the Vor Fru Hospital during the past seven years. The operative mortality of transurethral resection was 3.8 per cent, and of prostatectomy was 9 per cent. Sixty-three of the patients were over 75 years of age.

Thesis III. Epiphyseolysis Capitis Femoris. The discussion was introduced by Henning Waldenström, Stockholm, and Poul Morville, Copenhagen.

H. Waldenström, Stockholm, stated that epiphyseolysis, gradual gliding, and dislocation of the epiphysis of the hip joint are synonymous terms indicating dislocation of the epiphysis caused by some deficiency of the solidity of the bone layer extending from the cartilage of the epiphysis to the metaphysis. The action of the muscles and the weight of the body cause dislocation of the epiphysis backward and downward, the cup-shaped epiphysis rotating around the metaphysis; the femur is pushed upward, rotating outward. Endocrine disturbances are probably the causative agents of this process. This assumption is supported by the facts that: (1) one-third of the cases occur in the adiposogenital type; (2) dislocation occurs only during puberty; (3) the affection is bilateral in one-fourth of the cases; and (4) two-thirds of the cases develop the disease without any external injury. The dislocation does not occur suddenly; there is a gradual slipping. If diagnosis be established early, proper treatment may give favorable results. Every boy or girl limping ever so slightly should be carefully examined, and if the slightest restriction of mobility is found, an x-ray examination should be carried out, including lateral films. The lower part of the epiphysis glides over the metaphysis, covering it like a claw. The epiphyseal line is broad. If the epiphysis heals at this stage and its position is securely fixed, the hip joint will become normal. As long as the endocrine disturbance persists, a renewed dislocation in one or the other direction may occur. In the lecturer's own experience 25 per cent of the cases were bilateral, and the epiphysis tended to shift its position for about one and one-half years, but not longer. Pressure against the epiphysis must be eliminated, especially at the beginning of the process, in order to permit the epiphysis to heal and become fixed as soon as possible. Adhesive plaster extension should be applied for two to three months. After this period the patient should walk with crutches and without weight-bearing on the injured extremity for four to eight months, and finally he should walk with the aid of sticks until the dislocation process stops, which, as a rule, occurs at the end of a year. It is important to allow some mobility within the hip joint. Adhesive plaster extension permits this, but plaster of Paris does

not. So-called reposition performed under anesthesia is usually unsuccessful and also carries a risk of destruction of the joint (caput necrosis) in 20 per cent of the patients. Skeletal traction by means of a wire through the femoral condyles, without internal rotation, may be used, but not for longer than ten days.

Poul Morville, Copenhagen, stated that epiphyseolysis usually develops gradually, but it may appear acutely following trauma in a patient with latent disturbances. The slipping process comes to a stop when synostosis between the caput and collum develops. Follow-up examination after two to fifteen years following treatment reveals that many cases are improved, but many also show disturbances. Some patients develop a secondary arthritis of the hip at an early age. There is doubt whether manipulation yields any better results than prolonged bed rest without any attempt at correction. Manipulation does not correct rotation between collum and caput; the apparent reposition is due to the collum's being pressed into the caput. Traumatic arthritis may develop. Treatment by extension probably interferes with synostosis between caput and collum. In mild cases with slight dislocation drilling through the collum femoris may help to stop the slipping and to develop synostosis within two or three months. In cases of moderate or extensive dislocations, traction should be applied for a short time followed by drilling. In neglected cases with extensive dislocation, osteotomy should be performed.

In the discussion, N. A. Nicolayson, Bergen, expressed the opinion that bloodless reposition is possible and is justified in cases of extensive dislocation, especially in cases with traumatic epiphyseolysis presenting a short history. He reported 18 cases, 9 treated by reposition and 9 by conservative methods. The cases treated by reposition exhibited more favorable results.

H. Camitz, Göteborg, stated that plaster of Paris may be applied in rare cases when the dislocation is not more than two or three weeks old. When conservative treatment is unsuccessful, osteotomy should be used to correct the external rotation.

H. Döhlen, Oslo, stated that tall, heavy individuals with weak body structure and clumsy movements present this affection. Treatment should vary with the duration of the dislocation. In a series of 10 cases, 6 had been treated after two months by reposition and application of plaster of Paris with excellent results; 1 case treated after ten weeks by reposition was unsatisfactory; and 3 later cases were not treated.

H. Thrap-Meyer, Oslo, reported epiphyseolysis in a father (bilateral) and son (unilateral). In both cases the disease appeared at the usual age and was occasioned by relatively light trauma. The son was treated by open operation, and after two years the bending capacity was satisfactory, but mobility in the horizontal plane was reduced.

P. G. K. Bentzon, Aarhus, presented stereoscopic roentgenograms to support his contention that reposition under anesthesia may be a proper procedure. None of his cases treated in this manner had manifested symptoms of insufficiency, nor did roentgenograms reveal pathologic changes. The method of treatment should not be evaluated on the basis of improperly treated patients who had been immobilized in plaster of Paris in a position of forced internal rotation and abduction. Criteria of successful reposition are unimpeded internal rotation and stereoscopic roentgenograms showing proper position. Arthritis does not occur after a properly performed and successful reposition, but it is likely to occur in untreated cases.

G. Bohmansson, Oslo, advocated the method of slow extension in cases of epiphyseolysis. If reposition is required, spinal anesthesia is preferred. The lecturer had inserted three or four metal bars for the purpose of support and maintenance of position in 4 cases. The results had been good in 2 of these.

A. Brekke, Stavanger, reported a patient who had remained symptom-free two years after bloodless reposition. Cases of extensive, acute dislocation following trauma are more suitable for bloodless reposition than those with a slow slipping process.

J. Waldenström, Falun, suggested that better results might be obtained if the patients could be centralized in orthopedic departments.

F. Langenskiöld, Helsingfors, opposed drilling and nailing and used reposition methods in only a few cases when extensive dislocations were due to severe trauma. As a rule his treatment consisted of the application of a walking apparatus which protected the joint.

Guidal, Copenhagen, stated that it is not clear which method of treatment is best. Genuine dislocations of the epiphysis are not suitable for operation. Osteotomy is indicated in neglected cases.

Henning Waldenström, Stockholm, stated that most of the roentgenograms which had been shown were taken in such a manner that no conclusions concerning the results of reposition could be drawn from them. Neither did they show any evidence that necrosis is common following reposition. If the epiphysis is closed or almost closed, as the majority of roentgenograms showed, an attempt at reposition could not cause necrosis, but neither is reposition possible at this stage in most cases. It appears, however, from the statements expressed in the opening lectures that so-called reposition causes necrosis and destruction of the joint in many cases.

P. Morville, Copenhagen, advocated gradual extension rather than reposition under spinal anesthesia for epiphyseolysis. The patient should be controlled and treated until the roentgenogram shows synostosis.

E. Platou, Oslo, read a paper concerning experiences with the Smith-Petersen acetabuloplastic procedure. This has been published in *Nordisk Medicin*, 1940.

F. Teilmann, Gram, reported a case of vertebra plana in a 5-year-old boy. Two Norwegians, Billov-Hansen and Heyderdal, described a case of this disease prior to Calvé's report. Not more than 20 cases have been reported, and most of them from Scandinavia. The disease is assumed to be an aseptic bone necrosis caused by some unknown factor. Diagnosis is established by the roentgenogram. The treatment is the same as for tuberculous spondylitis. The prognosis is good. The patient should be carefully controlled when he becomes ambulatory and when he is permitted to discard his corset.

In the discussion, Halfdan Sundt, Stavern, stated that it is difficult to decide whether such cases should be treated at all. Most of them show complete clinical recovery whether they are treated or not. Protection of the affected area is one of the important points of treatment. He had seen 1 patient with this condition.

Sven Johansson, Göteborg, pointed out that steel is the most widely used material for osteosynthesis because of its strength and resistance to corrosion. He had experimented with various types of chromium-nickel steel and had found that an alloy, including 60 per cent nickel, 15 per cent chromium, and 16 per cent iron, was most suitable. The resistance to corrosion was measured by placing the material into a physiologic solution of salt containing 1 per cent of gum arabic and 0.02 per cent of potassium ferriocyanide. The amount of ferroferriocyanide produced was determined colorimetrically.

Elnar Ljungren, Sollefteå, discussed the diagnosis and treatment of tuberculous epididymitis and reported 68 cases treated at the Maria Hospital in Stockholm (Key). In 34 cases the affection was associated with tuberculosis of the kidneys, and renal lesions always should be sought for in cases of tuberculous epididymitis. The primary genital lesion frequently is in the prostate or seminal vesicles. Urethrographic examination is important, and in 28 patients it showed 14 cases

with cavity formations in the prostate. Most of the patients were treated by epididymectomy, if possible, or by orchiectomy. Early operation is desirable. General hygienic and dietetic measures should be applied. Twenty-seven per cent of the cases treated by operation died within five years, most of them from tuberculosis.

In the discussion, J. Hellström, Stockholm, stated that, if the diagnosis of tuberculous epididymitis is doubtful, epididymectomy should be performed. Even septic epididymitis sometimes develops very slowly. Patients suffering from epididymitis frequently respond well to injections of neosalvarsan.

Helge B. Wulff, Lund, discussed the treatment of tuberculous lymphadenitis of the neck, based upon a series of 222 cases treated by surgery (100 cases) or by x-ray (122 cases). The patients were followed for periods of six to ten years. The recurrence rate was the same for both groups (13 per cent). Seventy-eight per cent of the cases treated surgically and 63 per cent of the cases treated by x-ray were cured. It is advisable to individualize when selecting the method of treatment.

Gunnar Nyström, Upsala, demonstrated a method of multiple nailing for fracture of the neck of the femur, which had been used in 30 cases at the Out-Patient Department of the University of Upsala. Comparatively small, stainless steel nails had been used. The method seemed to carry less risk of dislocation of the fragment and of the nail than in the case of the Smith-Petersen nail.

In the discussion, J. Hellström, Stockholm, stated that, among 99 cases of osteosynthesis for fracture of the neck of the femur at the Maria Hospital, the following complications had been observed. In 8 cases the head had rotated when the nail was driven in; necrosis of the head had occurred 5 times; the nail had broken in 1 case six months after the operation; the nail had been driven into the acetabulum in 5 cases and had slipped out 16 times. Such complications might be avoided by applying the method proposed by Nyström.

Anton Poulsson, Oslo, demonstrated an apparatus for directing the nail in cases of fracture of the neck of the femur. It had been used in 42 cases, and in every case an ideal position had been obtained at the first operation.

In the discussion, B. Bager, Stocksund, pointed out that he had described a simplified method of osteosynthesis in *Der Chirurg*, 1939.

G. Levander, Köping, described the operative treatment of pseudoarthrosis by transplantation of living bone tissue. He used a paste made of thin strips of bone chiseled from the lateral aspect of the tibia and bone flour and blood obtained by drilling. This was applied to the defect in the bone. In 5 cases treated by this method there was satisfactory bone repair. The healing process required about two months.

N. Silfverskiöld, Stockholm, summarized the characteristic features of tumors of the synovia. They develop very slowly and present diagnostic difficulties. They show a tendency to metastasize, and the prognosis is grave. Amputation should be performed immediately upon making the diagnosis, and postoperative radium therapy should be applied to the regional lymph nodes. The author had seen 3 cases of synovial tumors.

Smith-Petersen, Boston, delivered a lecture concerning arthroplasty of the hip by a method based upon a new surgical principle.

The next Congress is to be held in Helsingfors in 1942. Professor Brofeld was elected president of this Congress. The following theses are to be presented: Thesis I. Arthritis Deformans From the Surgical and Orthopaedic Point of View; Thesis II. Acute Surgical Diseases of the Abdomen Associated With Pregnancy; Thesis III. Peripheral Vascular Disease, With Special Consideration of Arthritis Obliterans.

The membership of the society is 538; 45 new members were accepted, 19 had died, and 11 had resigned.

The author takes this opportunity to thank Dr. George S. Bergh, of the Department of Surgery of the University of Minnesota, for reading the manuscript and improving upon the dictation.

## Book Reviews

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*Diagnosis and Treatment of Head Injuries.* By Sidney W. Gross and William Elsbach. Cloth. Pp. 273, with 94 illustrations. New York, 1940. Paul B. Hoeber, Inc. \$3.

The authors state that this book attempts to present to the physician or surgeon of average training a practical and concise approach to the problem of head injury.

Beyond doubt, this purpose has been accomplished. The book is concise and thoughtfully developed. Brevity is attained by careful elimination of subject matter rather than by uniform abridgement of a great number of headings. There are some changes, however, which the authors may wish to make in later editions.

The chapters dealing with the gross anatomy and physiology of the brain could well be expanded to furnish a better understanding of the controversial aspects of treatment and the chapter on gunshot injuries might well be enlarged with material from the War Abstracts.

The chapter concerning surgical technique is of questionable propriety or value. Technique cannot be well learned from so brief a text as this and it is doubtful that such technique would be usable by the average practitioner to whom the book is devised.

The general principles of treatment are stated with due consideration for the conflicting current ideas and the discussion of extradural and subdural hemorrhage is comprehensive, clear, and remarkably complete for so small a book.

Considered as a compendium, the book is valuable and interesting, and with its bibliography provides an excellent introduction to the field of craniocerebral trauma.

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*Obstetrics in General Practice.* By J. P. Greenhill, M.D. Cloth. Pp. 445, with 118 illustrations. Chicago, 1940. The Yearbook Publishers. \$3.50.

This book cannot, as Greenhill admits in his preface, compete with the standard textbooks on obstetrics. It does cover, however, the basic facts of obstetric care and the more commonly encountered obstetric complications. There can be no doubt that the present high maternal and fetal mortality rates are due in large measure to the imperfect knowledge of these fundamental principles. They are here presented in easy style and generally as well-recognized facts, being shown of historical data, anatomy, and pathology. Certainly, if all the contained data were known and practiced by each physician doing obstetrics as a part of general practice, there should be definite improvement noted in statistical expressions of obstetric care. However, there can be no justification for a book of this kind other than that some uninformed members of the profession might refer to it rather than acquire a broader knowledge from one of the more thorough standard textbooks.

The chapter on ante-partum care is particularly wholesome in that it emphasizes the responsibilities of the one accepting the obstetric patient. Thoroughness as a routine is emphasized throughout this chapter and he who is unwilling to do this should not be intrusted with the lives of two individuals in a single case.

Conservatism is suggested in treatment of almost all obstetric complications and therapeutic abortion for active pulmonary tuberculosis is frowned upon. However, the suggested radical treatment of missed abortion would seem to have little to justify it in the light of infrequent or absent serious complications. The suggested conservatism with analgesia and anesthesia is a timely warning and well-founded reasons are given for the use of local infiltration and for keeping analgesia at a minimum. Up-to-the-minute classification of the toxemias of pregnancy and treatment of pyelitis and puerperal infection with chemotherapy are included. Of particular importance is the thorough treatment of hydatidiform mole with curettage followed by prolonged biological tests for evidence of chorionepithelioma.

The general tone of the whole book is one of simplicity, often to the point of sacrificing such strict and fundamental terminology as presentation of the fetus and presenting part.

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**Proctoscopic Examination and Diagnosis and Treatment of Diarrheas.** By M. H. Streicher, M.D. Pp. 149, with 39 illustrations. Springfield, Ill., 1939, Charles C. Thomas, Publisher. \$3.

This is a single volume monograph of 149 pages, comprising seven chapters. It is printed on good paper and is very readable.

Under "Armamentarium" various instruments are suggested. I feel that there are many instruments that the author uses efficiently, the ones with which the operator is most familiar being the ones he should use. The man doing general work should familiarize himself with instruments as outlined. The importance of doing proctoscopic examinations is stressed, as it certainly should be, for there is no part of an examination so commonly neglected. The author's preparation and technique for proctoscopic examination are well described. Lesions are discussed and case reports are cited and treatment outlined. This volume is well illustrated with drawings and x-ray film reproductions. While not presenting anything particularly new, it is well worth reading and will not require more than part of an evening. The insistence on the examination of the rectum is commendable.

# SURGERY

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## Original Communications

### JEJUNOSTOMY FOR THE RELIEF OF MALFUNCTIONING GASTROENTEROSTOMY STOMA

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OBSTRUCTION at the anastomatic stoma following gastroenterostomy or gastric resection occurs with considerable frequency and is a very serious complication. Numerous contributions have appeared in the literature attempting to explain its origin; yet, the cause is variable and usually not evident. Obstruction, therefore, cannot be prevented with certainty and, when it appears, the surgeon must treat it promptly and correctly to avoid a fatal outcome. Since we have had to deal with this complication so often, we believe it is worth while to record our experiences with the method of treatment that we have found to be most satisfactory.

Since postoperative obstructions should theoretically be relieved by correcting the cause or prevented by avoiding certain pitfalls, some attention must be paid to the various known ways by which obstruction may be produced. *Mechanical deficiencies* in the anastomosis occasionally cause malfunction. One of the loops of intestine may be twisted so that an actual kink is made. Sutures uniting the transverse mesocolon to the stomach above the line of anastomosis may give way or not be properly placed, allowing a segment of small bowel to herniate through the open trap. The position of the anastomosis, the direction of the opening in the stomach wall, the question of an iso- or retroperistaltic direction of the jejunal loop, and the length of the proximal limb of jejunum have all been more or less settled by laboratory data and clinical experience. The usual method in use in our clinic is a short loop anastomosis with proximal jejunum sutured to the lesser curvature in a more or less vertical direction at the junction of the middle and lower thirds of the stomach. Posterior anastomoses have been more popular than anterior, both with gastroenterostomy and following partial gastrectomy. The use of lightweight rubber-covered clamps has been the

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routine, since years ago it was felt that heavier elamps, on occasion, did cause thrombosis of blood vessels with subsequent edema and malfunction. Two layers of fine chromicized catgut have been used in most of the cases; some have had three rows of catgut and a few anastomoses have been done with interrupted fine silk. Increasing experience has diminished the number of mechanical obstructions so that, in the series we are reporting, only one patient could be considered to have suffered from any technical error at the time of the original operation.

*Adhesions associated with a plastic peritonitis* of low grade near the suture line have frequently been considered a cause for malfunction of the stoma. They are present, however, to some extent in nearly every case and, since some stomachs empty completely in spite of them, it offers a poor explanation for the anastomoses that do not function at all. In other words, it seems obvious to us that this is not often, if ever, the sole cause of trouble. We must include here the possibility of a dense adhesion between a segment of small bowel and the region of the anastomosis or raw fatty edge in the transverse mesocolon opening. Such could obstruct the bowel at the level of the adhesion and without herniation. This makes it necessary to re-explore the abdomen at the time of jejunostomy to avoid overlooking this rare cause for obstruction.

*Acute dilatation of the stomach* distorting the anastomosis is now practically unknown, due to the routine use of the Levine tube. The tube is inserted before the operation and left in place for forty-eight to seventy-two hours afterwards. Its removal is dependent upon evidence of an adequately functioning anastomosis. Atonia of the stomach has also been blamed as a cause for its failure to empty. This is not uncommon, especially in the patient who has had a long period of preceding obstruction before the primary operation on the stomach. Such a patient may clear up his obstruction remarkably on a highly seasoned solid diet, when all previous efforts had resulted in persistent lack of peristalsis.

*Biochemical Factors.*—The most tenable theory is that elaborated by Ravdin.<sup>1</sup> He believes obstruction of the anastomosis is due to edema and emphasizes, with Jones and Eaton,<sup>2</sup> the importance of subclinical states of hypoproteinemia in the production of edema and malfunction. We agree that obstruction is probably often due to edema in the region of the stoma. However, the serum protein measured in the usual fashion is normal in most of the patients with the complication under discussion.

Despite these numerous theories, the actual situation found at secondary operation is apt to reveal no satisfactory explanation of the difficulty. Preoperative studies will usually show blood chemistry determinations to be within normal limits. At laparotomy, the stomach will be found to be small and not distended. A few loose adhesions will usually be seen about the anastomosis, but they rarely can be considered to have any bearing on the situation. The surgeon may well be perplexed, since he has operated for a very serious complication and has

found nothing to explain it satisfactorily. However, numerous procedures to correct the fault are available. *Enteroenterostomy* between the afferent and efferent loops of jejunum was a favorite procedure in earlier years. It involves, however, many difficulties. Plastic adhesions about the anastomosis have to be broken up in order to identify the exact segments of jejunum. When a short loop posterior anastomosis has been made, the length of the afferent portion of jejunum may be too short to perform this operation satisfactorily. *Enteroenterostomy* in cases of duodenal ulcer carries the hazard of marginal ulcer after the patient has recovered from his original operation. For this reason alone, we believe it should never be done except when dealing with carcinoma associated with achlorhydria.

A second gastroenterostomy is another procedure that has been employed. If the original anastomosis has been placed posteriorly, an anterior gastroenterostomy is tried. The obstruction tends to recur in the new anastomosis from the same factors that caused it in the primary stoma. It is only of value in case there has been some actual mechanical misadventure at the time of the original gastroenterostomy.

*Duodenojejunosomy* has been performed to relieve malfunction, uniting the third portion of the duodenum to the descending loop of jejunum. This is accomplished after the duodenum is exposed through the transverse mesocolon. It may be a difficult operation and is open to exactly the same objections as an enteroenterostomy.

*Gastrostomy* was a favorite procedure of some of the continental surgeons before the Levine tube became popularized; this took the tension off an overloaded stomach and allowed edema to subside and the anastomosis to function. Some authorities, such as Perman,<sup>3</sup> have considered this operation to be the most satisfactory method of dealing with obstruction.

It has been suggested that postoperative obstruction will not occur if an inlying tube of the Abbott-Rawson<sup>4</sup> type is used, one portion of the tube being left in the stomach while the other enters the efferent loop of the jejunum extending well past the anastomosis. By this means, the stomach contents may be aspirated and immediately returned to the jejunum; also, it has the advantage that early feedings may be introduced into the jejunum. While this may be of value in some cases, the fact that when true obstruction occurs, three weeks usually elapse before the stoma reopens, means that the nasal tube would need to be retained for this long period in those very cases in which it is most desperately needed. Such continuous retention of the nasal tube is not only uncomfortable to the patient but has definite hazards, aside from an irritating pharyngitis. Iglaue and Molt<sup>5</sup> have reported several instances of a necrosing laryngitis requiring tracheotomy for relief. It is also very difficult to retain a nasal tube over a long period of time if the patient has any pulmonary complications at all.

*Jejunoplasty* has recently been proposed by Hoag and Saunders<sup>6</sup> as a method of treatment. This involves actual exposure of the anastomosis with a plastic procedure upon the stoma. We have had no experience with this operation. It is of considerable interest but involves a rather extensive dissection on a patient that is very ill. Follow-up studies on patients treated by this method may show that marginal ulcer will follow as frequently as it does after enteroenterostomy.

*Jejunostomy* has also been used extensively. It has not been a popular operation until recently. This is probably due to the fact that the inlying nasal tube was not employed in earlier years. Thus, Perman<sup>3</sup> found that the mortality following jejunostomy for stomal obstruction was 80 per cent in his series. The procedure, however, has evoked considerable interest in this country. Gibson<sup>7</sup> in 1900 performed jejunostomy as an adjunct to operations on the stomach in order that the patient might be fed at an early period. Its use in the treatment of postoperative obstruction of the stoma has been advised by Graham,<sup>8</sup> Walters and Hartman,<sup>9</sup> Pfeiffer,<sup>10</sup> and Clute.<sup>11</sup>

Jejunostomy, then, is one of the oldest operations devised for the malfunctioning stoma. Its advantages are: (1) the simplicity of the operation; (2) the fact that the gastrojejunal anastomosis is left in the exact condition that it was planned originally; (3) the fact that it effectively maintains the patient's nutrition until edema of the anastomosis subsides and obstruction is relieved. However, attention must be paid to the details and indications for this procedure in order that its application may be successful. We believe it is not jejunostomy itself, but jejunostomy that is performed according to certain indications and in a certain fashion that constitutes the best method of dealing with postoperative obstruction of the stoma.

The material from which these data have been drawn has been collected from the cases observed in the Massachusetts General Hospital from the years 1936 to 1940, inclusive. The first four cases in the series have been treated by us personally and the others by various surgeons on the staff (Table I). The actual technical procedures often varied considerably so that conclusions may be drawn with regard to the best method. We shall attempt to set down a critical analysis of our experience with this operation.

In our clinic jejunostomy has been employed as a preliminary procedure to operations upon the stomach, as a concomitant operation to gastric surgery being done at the same time, and, third, as a measure for the relief of postoperative obstruction. The performance of preliminary or concomitant jejunostomies has been urged as a measure to improve general nutrition and thus prohibit or decrease the number of postoperative complications. Preliminary jejunostomy is not without its hazards. We have found that, if the stoma is placed too low in the flank, it may constitute a fixed point about which the small intestine may herniate,

TABLE I  
FREQUENCY OF POSTOPERATIVE OBSTRUCTION

TYPE OF OPERATION	OPERATIONS	JEJUNOS- TOMIES	FREQUENCY OF OBSTRUCTION
Gastrojejunostomy			
Posterior	73	7	9.7%
Anterior	11	0	--
Gastric resections			
Posterior gastrojejunal anastomoses (Pólya, Billroth II, Hofmeister)	162	5	3.1
Anterior gastrojejunal anastomoses (Pólya, Hofmeister)	24	1	4.1
Gastroduodenal anastomoses (Billroth I, gastroduodenostomy)	7	2	29.0
Pyloroplasty	5	0	--
Total	282	15	5.3

producing intestinal obstruction. Jejunostomy performed in the Witzel fashion has actually been found to have obstructed the portion of small intestine proximal to it. Also, it requires usually about three weeks of jejunostomy feeding before any actual improvement can be noted in the patient's general condition. Often one cannot measure this improvement since the laboratory findings and weight chart may remain unchanged. There can be no doubt that such patients do withstand a large resection better if the ingestion of food has been interfered with for some time before. It probably should be used with greater frequency.

Concomitant jejunostomies have been used almost routinely with total gastrectomies in our clinic and occasionally in patients who appear to be poor operative risks from prolonged starvation. Further experience may show that we should employ it more often than we do now. It prolongs the operating time only a few minutes and often shortens the convalescence materially.

It is possible that the number of postoperative jejunostomies may be diminished by attention to the special patients who are likely to develop obstruction; in such cases jejunostomy should be done concomitantly with the original operation. Thus, the percentage of obstruction following posterior gastroenterostomy is considerably higher than it is following resection of the stomach. Patients with thick fat mesocolons are prone to develop obstruction, especially if the posterior anastomosis is employed. Secondary operations, as for stomal ulcer, carry more hazard if the mesentery of the jejunum is very short so that an anterior anastomosis cannot be made. Placing the new anastomosis through the unavoidably scarred and traumatized opening in the mesocolon is conducive to malfunction. Such patients may do well to have a jejunostomy at the time of the original operation.

Assuming that operation has been performed and jejunostomy has not been done, the patient must be carefully observed for any signs of

postoperative obstruction. The iulying nasal tube is allowed to drain by gravity and is aspirated at least every two hours. The patient is given nothing by mouth on the day of operation, an ounce of water an hour on the next, and two ounces on the second day. The fluid taken in by mouth is carefully noted and compared with the amount that is aspirated from the Levine tube. If the amount swallowed exceeds that withdrawn, the gastric balance is said to be positive; on the other hand, if the patient puts out more fluid through his nasal tube than he takes by mouth, his gastric balance is said to be negative. In the usual case, there is a slight negative balance of 100 to 200 c.c. during the first forty-eight hours; the balance then becomes positive and remains so. Patients who are to develop obstruction will often show

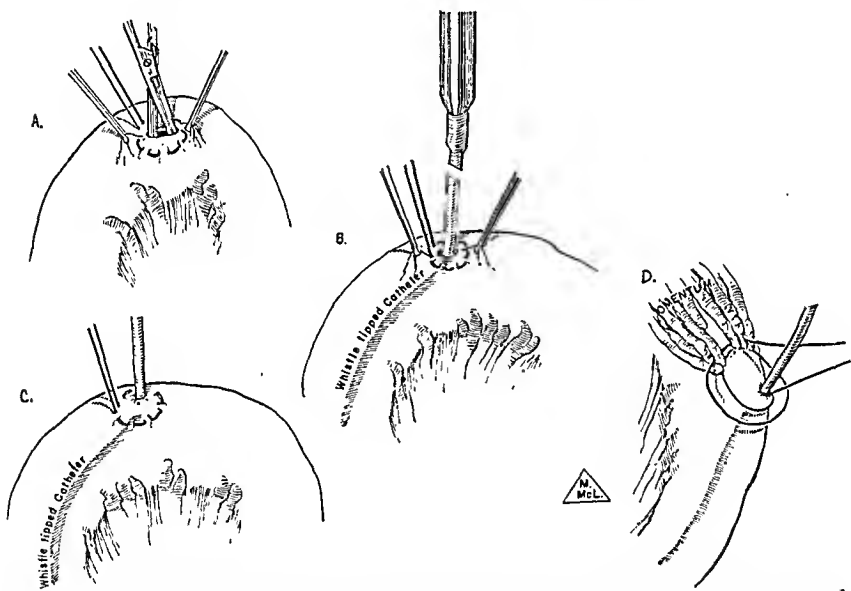


Fig. 1.—Technique of jejunostomy: *A*, a purse-string suture has been inserted and the jejunum is opened with scissors. *B*, the catheter is inserted, passage being facilitated by introduction of saline solution through a syringe. *C*, a second purse-string suture is made. *D*, omentum is brought about the tube.

as great a negative balance as 1,000 c.c. on the first postoperative day. This immediate obstruction is by far the most common type. Other patients soon have a positive balance; the nasal tube is withdrawn at the usual time and then suddenly on some later day obstruction is discovered. The sixth to the eighth day is the most common time for delayed obstruction to appear; however, it must be emphasized that signs of obstruction usually date from the time of the original operation. Its presence is often clouded by clinical optimism or by failure to employ daily aspirations to test the gastric residual.

If the gastric balance is negative and obstruction is definitely present, it is wise to watch the patient for a short period of time. Many patients will have only a small negative balance for a few days, in-

diating that a large proportion of the gastric contents are passing through the anastomosis. In such cases, further conservative therapy is indicated. Other patients run a negative balancee from 1,000 to 3,000 c.c. daily; they should be regarded as completely obstructed and reoperation is indicated at an early date. Long-continued negative balancees, even though they be small in amount, are likewise extremely dangerous and often must be corrected by reoperation. From a study of our cases, we have obtained the impression that the great danger is the omission of this operation until too late. The hazard does not lie in the procedure itself but in delay, during which time the patient's resistance is lowered and he becomes prey to other complications. Thus, patients dying of late obstruction die of pulmonary complications as a general rule; they must be regarded as much poorer risks than their general condition indicates or than their blood chemistry tests may show.

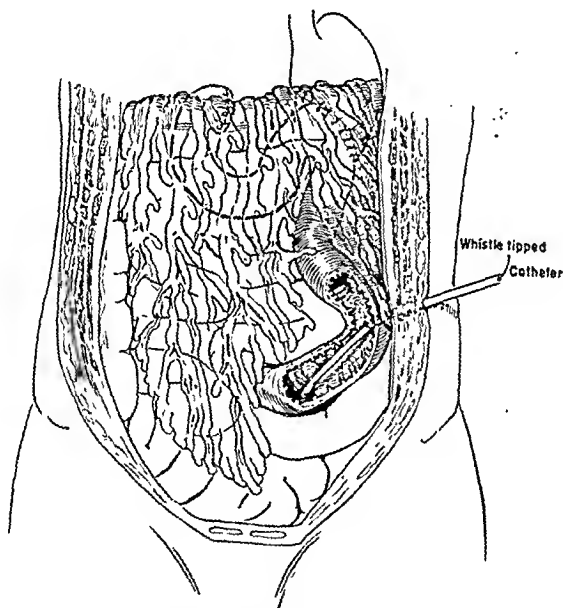


Fig. 2.—Diagram illustrating the final position of the jejunostomy catheter.

To wait until the patient actually needs the jejunostomy to maintain his general condition is to wait too long. This is especially true in the older age group. The mortality of obstruction in the patients whose age is 50 years or over is nearly 50 per cent, while none in this series have succumbed to that complication who were under the age of 50 years. In addition, all patients above 50 years of age who had reoperation before ten days of obstruction had elapsed recovered; while of the five patients who had reoperation after ten days or more of obstruction, there was only one recovery. With the younger age group in whom resistance is higher, operation can be deferred for a comparatively long period of time without fatal outcome. We believe that reoperation should be done in the older age group a week after obstruction has oc-

curred, while with those patients under 50 years of age it may be deferred for a few more days if the patient is in good condition and if there are clinical and laboratory data that offer hope of further improvement.

It is sometimes desirable to prove the diagnosis of obstruction by the oral administration of a little barium followed by fluoroscopic observation. The barium usually passes slowly through the anastomosis and then entirely stops about one inch below the stomach in the region of the efferent loop. Occasionally under the fluoroscope one may find that a certain posture enhances the passage of stomach contents into the efferent jejunal limb and, by utilizing this position after feedings, the situation will gradually clear up.

When reoperation is performed, certain technical details are extremely important. Spinal anesthesia, evipal, or local novocain block may be used. An adequate incision is necessary. We believe the best approach may be gained by reopening the previous operative wound. This will allow inspection of the anastomosis and elimination of any mechanical cause of nonfunction. Correction of such a mechanical cause, if found, should be supplemented by a jejunostomy. Plastic adhesions about the anastomosis should not be divided since they will only re-form in a more dense fashion. The efferent loop of jejunum should be accurately identified and visualized over a distance of 18 inches below the site of the anastomosis. It must be ascertained that there are no bands obstructing the intestines below this point.

The most common errors of jejunostomy will have been avoided by these details. Often one is tempted to wait until the patient is in such precarious condition that he will stand no other anesthesia than a little novocain in the abdominal wall. Through a tiny subcostal incision, an attempt is made to define the efferent loop; it is usually impossible and a tube is placed in a portion of the jejunum that may be entirely unsatisfactory. One case in this series had definite obstruction from a point below the site at which the tube was inserted so that the jejunostomy did more harm than good.

The loop of jejunum selected for insertion of the tube must be one that will lie comfortably just beneath the left costal margin in the nipple line without any tension on either the upper or lower limbs; usually this is about twelve inches below the anastomosis. The site selected for the stab wound must not be too low or too near the midline, since the small bowel may rotate about the fixed point if the intestine is carried away from its natural position. The jejunum is carefully protected by moist gauze packs and a purse-string suture of No. 00 chromic catgut is introduced. The jejunum is then opened at this spot and a No. 16 French whistle-tipped catheter inserted. The tip of the catheter must point distally down the jejunum. It is extremely easy to direct it the opposite way unless care is taken. Introduction of the catheter is often facilitated by the gentle insertion of normal salt solution through the catheter with an aseptic syringe during the time the tube

is being inserted into the bowel. After six inches of the catheter have been placed within the jejunum, the purse-string suture is tightened and then carried through the wall of catheter to anchor it in position. This first suture is then buried by a second inverting purse-string suture placed about the catheter not more than one-fourth inch outside of the original. The catheter is then brought through a small opening which is made in the great omentum and out through the stab wound in the left subcostal area. There should be no kinking of the jejunum at the time the abdomen is closed. We have tried bell-tipped catheters for jejunostomy and given them up since they have no advantage over the whistle-tipped tube and on one occasion at least failed to function due to compression of the flange by the purse-string suture.

We have found this to be a much more satisfactory procedure than the Witzel type of jejunostomy. The Witzel method in a bowel of normal size will reduce its lumen quite markedly so that the added edema of operation may produce subacute obstruction. This occurrence has been noted occasionally in patients on whom this type of jejunostomy was done as a preliminary procedure to gastric resection. The Witzel jejunostomy is also more difficult and time consuming to perform. It possesses no advantages over the simple purse-string jejunostomy. Following the removal of the catheter in either type, leakage from the abdominal sinus will cease almost immediately.

Following the jejunostomy, the surgeon is then committed to what may seem to him to be an interminable period of waiting until the edema about the original anastomosis subsides and stomal obstruction is relieved. During this period, he will probably attempt many variations of the oral intake in an attempt to relieve the obstruction. However, relief is a matter of time rather than any other factor. The surgeon must possess the courage to realize this fact and to persist until obstruction is finally overcome. In our cases this has occurred any time from fourteen to fifty days after the resection. The average length of time after jejunostomy before obstruction is relieved is twenty-two days in this series.

It is important that the patient's nutrition be maintained during this period of time and the stomach kept empty by an inlying nasal tube. If the nasal tube becomes uncomfortable, repeated gastric aspirations may be employed instead. The matter of feeding through the jejunostomy tube in our experience has been a totally individual problem. No one diet that can be specified for one person is apt to be satisfactory for another. There are a few features that are important, however. The first is that so far as possible it is wise to return the contents aspirated from the stomach into the jejunum. Occasionally, at certain stages, it may be possible to allow the patient to have a certain amount of food by mouth, withdraw the partially digested contents, and return them to the jejunum. In the early stages of feeding, milk and lime water mixed in equal parts are usually best tolerated. Saline solution often starts a

severe diarrhea; this may be avoided by the use of tap water as a basis for any feedings that are employed. After the jejunum tolerates simple liquids, the caloric intake may be increased and varied.<sup>12</sup> Any suitable food that can be divided finely enough to be forced through the tube can be given. The exact diet is quoted in one of the cases cited at the end of this article in order that its variegated nature may be apparent. Any tendency to diarrhea is easily controlled by an occasional teaspoonful of paregoric inserted in the jejunostomy tube or added to the feedings. We formerly used tincture of opium for this purpose, but paregoric as suggested to us by Graham\* is more effective. The urinary output can be kept at a satisfactory level usually by the jejunostomy feedings; if, however, it is not adequate, intravenous saline solution can be used.

Frequent determinations must be made of the blood chemistry. The nonprotein nitrogen has remained normal in about half our cases, but in the other half has risen appreciably. In certain cases this has definitely been the effect of an underlying chronic nephritis; in others the nonprotein nitrogen seems to have risen for no apparent reason. The serum protein will usually require maintenance by means of repeated transfusions, although after protracted jejunostomy feedings sufficient protein may be acquired in this fashion to maintain an adequate level. The serum chloride will often be found to fluctuate and this again can be easily controlled by means of either intravenous saline solution or distilled water, as the case may indicate.

Patency of the stoma may finally be determined by use of the barium meal. As soon as the gastric balance becomes positive, improvement is extremely rapid. The jejunostomy tube is usually removed a few days after the gastric balance is satisfactory. After the patient has definitely improved, it is well to withhold jejunostomy feedings for twelve hours periodically. Unless this is done, one may find the stoma widely open and ready for mouth feedings in spite of an apparent negative balance. This is explained in two ways: some of the jejunostomy feedings regurgitate into the stomach and are withdrawn through the Levine tube; also, there must be a physiologic need for food to pass through the stoma and the upper jejunum must be empty before this need asserts itself.

The cases that we have treated by jejunostomy are summarized in Table II and are abstracted briefly at the conclusion of this article. We have found that obstruction, which is first noted immediately after operation and in which a negative gastric balance continues from that time on, is the most serious type. On the other hand, those cases in which the gastric balance is first positive for six to eight days and obstruction then follows have a comparatively good prognosis. Patients with immediate complete obstruction will practically always require a jejunostomy for relief at an early date if they are to survive. If the obstruction develops late, conservative procedures, such as repeated gastric aspirations and a reduction in the fluid intake by mouth,

TABLE II\*

NO.	AGE	DATE OF OBSTRUCTION	DATE OF JEJUNOSTOMY	DURATION OF OBSTRUCTION BEFORE JEJUNOSTOMY	DATE OF RELIEF OF OBSTRUCTION	DISEASE†	OPERATION	RESULT
1. C. H.	45	6th day	12th day	6 days	42nd day	D. U.	Resection, posterior Hofmeister	Lived
2. F. B.	42	Immediately	8th day	8 days	30th day	D. U.	Posterior gastroenterostomy	Lived
3. R. C.	64	Immediately	9th day	9 days	25th day	D. U.	Posterior gastroenterostomy	Lived
4. F. K.	51	Immediately	5th day	5 days	14th day	D. U.	Posterior gastroenterostomy	Lived
5. C. H.	66	8th day	14th day	6 days	50th day	D. U.	Resection, anterior Hofmeister	Lived
6. M. B.	24	(?) Immediately	15th day	15 days	32nd day	G. U.	Resection, Billroth I	Lived
7. S. S.	70	Immediately	5th day	5 days	31st day	Ca. stomach	Posterior Pólya resection	Lived
8. H. B.	50	Immediately	7th day	7 days	26th day	D. U.	Resection, Billroth I	Lived
9. S. B.	34	Immediately	13th day	13 days	31st day	D. U.	Posterior gastroenterostomy	Lived
10. M. D.	74	Immediately	13th day	15 days	27th day	Ca. stomach	Posterior gastroenterostomy	Lived
11. J. A.	62	10th day	15th day	5 days	25th day	Ca. stomach	Posterior Pólya resection	Lived
12. G. L.	59	Immediately	15th day	15 days	—	Ca. stomach	Posterior Pólya resection	Died
13. W. I.	70	4th day	16th day	12 days	—	Ca. stomach	Posterior Pólya resection	Died
14. C. C.	60	Immediately	17th day	17 days	—	D. U.	Posterior gastroenterostomy	Died
15. J. L.	60	6th day	17th day	11 days	—	D. U.	Posterior gastroenterostomy	Died

\*Dates are all estimated from day of original operation.

†D. U., duodenal ulcer; G. U., gastric ulcer; Ca., carcinoma.

will often produce relief without the necessity of surgery. Two or three days of conservative treatment are often enough in the latter group, but not over a week of obstruction should be allowed to pass before a jejunostomy is done. It is impossible to estimate accurately from our records the number of patients who have a mild temporary obstruction from which they recover without surgery. It is our impression that about as many patients are treated in a conservative fashion as require reoperation. In all of these mild cases there has been no prolongation of the usual hospital stay and in only a few of them were symptoms marked enough to require any notation in the progress notes. No deaths occurred in this group in which obstruction could have conceivably played a role.

On the other hand, all the severe forms of obstruction were treated by reoperation. All of the reoperated cases, with one exception, had a jejunostomy performed and are summarized in the clinical abstracts. The other case recovered after an enteroenterostomy, a complete kink of the efferent loop having been found at reoperation. This is the group which, according to Hoag and Saunders,<sup>6</sup> has an expected mortality of 60 to 75 per cent.

In our series of 15 cases treated by jejunostomy, 5 patients had carcinoma of the stomach, while 10 had an ulcer, of which 9 were duodenal and 1 gastric. Half of the obstructions followed posterior gastroenterostomy. Five followed resections with posterior anastomoses (4 Pólya, 1 Hofmeister), 1 followed resection and an anterior anastomosis of the Hofmeister type, and 2 followed a Billroth I procedure. When comparison is made with the number of these operations done in the clinic during the same period, it is shown that in this series gastroenterostomy was definitely more likely to be followed by obstruction than were the resections with posterior anastomoses. In our series of gastric operations in the last five years about 1 patient out of 10 developed obstruction following a posterior gastrojejunostomy, while about 1 out of 30 had the same complication after resection and posterior anastomosis. The frequency of postoperative obstruction, therefore, has been three times greater after posterior gastroenterostomy. Our experience with anterior anastomoses either of the Hofmeister or Pólya has not been extensive, but obstruction does not appear to be less common. This is due, in part, to the use of anterior anastomoses in certain cases described above in which posterior anastomosis would have been almost sure to cause obstruction. It is interesting that the number of postoperative obstructions following the few Billroth I resections were comparatively high; this has been emphasized frequently in the literature.

Ten of the patients had definite negative gastric balances beginning on the first postoperative day and continuing thereafter until operation was performed. Five of the patients in whom the obstruction developed at a later period required jejunostomy.

In the group of patients 50 years of age or under, there were no postoperative deaths. All of them had ulcer. The secondary operation was performed from five to fifteen days after obstruction had been noted. In other words, it seems that the young patients are comparatively good risks and will occasionally tolerate a long period of obstruction.

Ten of the patients were over 50 years of age; 5 of them had ulcers and 5 had cancers of the stomach. Two of the ulcer patients and 2 of the cancer patients died. The ultimate result then did not seem to depend so much on the underlying disease as it did on the fact that of the patients who had the jejunostomy performed under less than ten days after the obstruction began none died; while of those patients who had it delayed over ten days, all succumbed with one exception. The length of time the obstruction persisted after jejunostomy was done seemed to bear little relation to the date that obstruction first occurred. In other words, while late obstruction is usually mild, it can be fully as persistent as the immediate type.

*Summary.*—Early postoperative gastric obstruction following gastroenterostomy or gastric resection is due, in nearly every case, to edema in the region of the stoma. Relief may be secured in several ways, but, if the patient can be kept alive and in good physical condition for a period that has varied from fourteen to fifty days in our series, the edema will subside and obstruction be relieved. The operation of choice for this complication is jejunostomy. It has been required for postoperative obstruction 15 times in a series of 282 gastric operations in the past five years in this hospital. Mild obstructions occur nearly as frequently but subside promptly and carry no mortality.

Large negative gastric balances beginning immediately after operation usually mean that reoperation will be necessary. Persistent negative balances, even if they are small, are nearly as dangerous. The important consideration is that the second operation be done at an early date while the patient is still in good condition. We believe that a week of obstruction is sufficient indication in patients over 50 years of age, while younger patients may be allowed a slightly further delay.

When jejunostomy is done, it should be performed through an adequate incision, preferably through the original operative wound. We advise a No. 16 French whistle-tipped catheter held in place by two closely placed purse-string sutures. The catheter is brought out through the great omentum and through a subcostal stab wound.

There were four deaths, indicating a mortality of 27 per cent in those patients obstructed severely enough to require reoperations. These four were all over 50 years of age and had had over ten days of obstruction before the jejunostomy was done.

## CONCLUSIONS

1. Early postoperative obstruction of the gastroenterostomy stoma may be allowed to continue a week if the patient is over 50 years of age, or slightly longer if he is young and in good condition.

2. Reoperation is indicated if obstruction still is present at that time.

3. The most satisfactory method of treatment is jejunostomy performed through the original wound with a No. 16 French whistle-tipped catheter placed in the jejunum by a purse-string technique.

## CASE HISTORIES\*

CASE 1.—C. H. (P. H. No. 1312), a 45-year-old male, was admitted to the hospital on Jan. 16, 1939, because of repeated gastric hemorrhages.

Seven years before he had had a transection of the pylorus and a posterior gastroenterostomy performed by another surgeon because of a bleeding duodenal ulcer. Postoperatively, despite adherence to a rigid diet, after a respite of three years, he began to have recurrent hemorrhages. During this period several x-ray examinations were made. There was never any evidence of a gastrojejunal ulcer. The gastric rugae were prominent. The barium left the stomach very slowly through the gastroenterostomy stoma. A gastric residue was still present at the end of twenty-four hours.

He entered the hospital this time two weeks after his last hemorrhage for consideration of surgery. It was thought that his bleeding originated from hypertrophic gastritis and that his stoma was too narrow to allow regurgitation of the contents of the duodenal loop.

Examination at entry showed a well-developed and well-nourished man. He weighed 160 pounds and was in excellent general condition. The physical examination was essentially negative. His blood pressure was 120/80; his pulse, 70. The red cell count was 3,970,000; white count, 6,700; and the differential count, normal. The bleeding time was 1½ minutes. The clotting time was 7, 13, 20, and 23 minutes in four tubes. Clot retraction was normal. The blood cevitamic acid was 0.6 mg. per cent; the plasma protein, 6.5 per cent. A liver function test was normal. The stools were negative to guaiac. A gastric analysis showed 36 c.c. of 1/10 normal HCl acid and 44 c.c. of combined after a test meal of 50 c.c. of alcohol.

Another x-ray examination showed evidence of gastritis, but none of ulcer. A gastroscopy was done by Dr. E. B. Benedict. The gastroenterostomy could not be visualized. There was a marked superficial and hypertrophic postoperative gastritis with erosions and hemorrhage.

Operation was performed on Jan. 30. Dense scar tissue was found about the stoma. The gastroenterostomy was identified. It was tightly constricted by a thick, porky mesocolon, nearly 2 cm. in thickness. The stoma was found in a high position, so that the antrum formed a kind of pouch, capable of holding nearly 500 c.c. There was no evidence of residual duodenal or a gastrojejunal ulcer. The lower two-thirds of the stomach, together with the stoma, were resected. An end-to-end aseptic anastomosis of the jejunum was made. A Hofmeister type of gastrojejunostomy was performed. Although the inflamed mesocolon made a posterior anastomosis unsatisfactory, it had to be done, since a short mesentery of the jejunum precluded an antecolic procedure.

\*Cases 1, 2, and 3 were mentioned briefly by the senior author (A. W. A.) in the discussion of the paper of Hoag and Saunders.<sup>12</sup>

The pathologic specimen measured 14 cm. along the lesser curvature and 21 cm. along the greater. The whole mucosa was covered with small ulcerations, many of which were bleeding. The microscopic report was subacute and chronic gastritis.

Postoperatively an indwelling nasal tube was left in place three days. During this time he daily put back 500 to 1,500 c.c. more through the tube than he took by mouth. The tube was withdrawn and he had no distress for three more days. On the sixth postoperative day the tube was replaced, and Wangenstein suction was instituted. He continued to run a negative gastric balance of nearly 1,500 c.c. daily.

His blood chemistry remained normal. On the twelfth day, since the stoma was obviously obstructed, the abdominal wound was reopened. There was a great deal of edema and many fresh adhesions about the mesocolon. The anastomosis was intentionally not freed. Two fingers could be passed into it from above, however. A jejunostomy was made with a No. 16 Pezzer catheter about eight inches below the ligament of Treitz, bringing the tube out through a small stab wound in the left subcostal area.

Thereafter he drained about 3,000 c.c. daily of stomach and duodenal contents through his nasal tube. This liquid was all returned to his intestinal tract, together with gradually increasing quantities of food. The diet was carefully calculated by Dr. B. H. Ragle. The jejunostomy tube functioned perfectly, he had no diarrhea at any time, and he gained weight. His blood chemistry and cell counts remained at normal levels throughout the convalescence. He received a total of three transfusions, one at the time of the resection and two at the time of the jejunostomy.

Eleven days after the jejunostomy the nasal tube was removed for several hours at a time, because of increasing irritation of the throat, and a little bleeding therefrom. He had tolerated it for sixteen days at that time.

His negative gastric balance slowly diminished. Fifteen days after the second operation it was still 500 c.c. A small amount of barium was given by mouth, and a trace could be seen to pass through the anastomosis. Twenty-seven days after the jejunostomy, feedings by the jejunal tube were entirely omitted, and on the following day nothing was obtained at any time from aspiration of the stomach. On the next day, forty-two days after the original operation, barium by mouth was seen to pass rapidly through the stoma under the fluoroscope. At that time he was tolerating a soft solid diet by mouth.

The jejunostomy diet, of considerable interest in this case, may be summarized as follows: (During this time he was receiving about 60 to 90 c.c. of water hourly by mouth to prevent parotitis or irritation from the nasal tube.)

Day of jejunostomy	Nothing.
First day	All of gastric aspirations (2,000 c.c.); 1 Gm. cebione; saline solution, 1,500 c.c.; betelin, 6.6 mg.
Second day	All of gastric aspirations (3,000 c.c.); 500 c.c. milk and lime water, 2 egg whites, and beef juice, 180 c.c.
Third day	All of gastric aspirations; 4 egg whites; beef juice, 240 c.c.; thin gruel and milk, 90 c.c.
Fourth day	All of gastric aspirations; 6 egg whites; beef juice, 270 c.c.; thin gruel and milk, 1,060 c.c.; liver pulp, 60 Gm. (820 calories).
Fifth day	All of gastric aspirations; 4 whole eggs; 60 Gm. liver pulp; 1 pint milk; 50 Gm. dextrose, cod-liver oil ziii. gruel; beef juice, 240 c.c. (1,790 calories).
Sixth day	All of gastric aspirations; same, but add 100 c.c. orange juice, 25 c.c. karo, and 20 c.c. dilute HCl (1,880 calories).

Tenth day

All of gastric aspirations; beef juice, 240 c.c.; liver pulp, 60 Gm.; 4 eggs; 500 c.c. milk; orange juice, 200 c.c.; dextrose, 50 Gm.; karo, 35 c.c.; cod liver oil, 20 c.c.; dilute HCl, 20 c.c.; 10 per cent NaCl, 50 c.c.; brewer's yeast, 1 dr.; mashed potato, 30 Gm.; purée spinach, 30 Gm.; tomato juice, 50 c.c.; butter, 20 Gm. or cream, 20 per cent, 100 c.c.; gruel, ad lib. (2,200 calories).

He was entirely free of symptoms a year later.

CASE 2.—F. B. (M. G. H. No. 205083) entered the hospital on July 25, 1939, with the diagnosis of obstructing duodenal ulcer. He was a 42-year-old sheet-metal worker, who had had a diagnosis of duodenal ulcer made five years before by x-ray, following a short period of epigastric pain. A month before entering, he began to vomit large amounts of fluid. X-ray studies showed partial obstruction at the pylorus, spasm of the antrum, gastritis, duodenitis, and an active duodenal ulcer. At a repeat examination, after twelve days of medical treatment, no barium could be seen to pass the pylorus during an hour's observation. Accordingly, operation was done. Under spinal anesthesia exploration revealed a very large, indurated mass in the region of the pylorus and antrum, which felt like inflammation rather than neoplasm. A routine posterior gastroenterostomy was done. There were a few adhesions in the region of the ligament of Treitz. A lumen of two or three fingers was obtained.

He immediately began to run a negative gastric balance, which varied from 500 to 1,500 c.c. daily. His blood chemistry showed no remarkable change, and he remained in good condition. On the eighth postoperative day he was again explored. The midline wound was reopened. There was no evidence of peritonitis. Nothing could be felt in the region of the gastroenterostomy to indicate the cause of the obstruction. A loop of jejunum was identified at a point about eight inches from the gastroenterostomy. A No. 16 catheter was inserted and fixed with two purse-string sutures, reinforced by omentum. The catheter was brought out through a stab wound in the left side.

Eleven days after the jejunostomy, he was gotten out of bed. Barium by mouth failed to pass through the anastomosis. Numerous measures were tried to maintain a normal blood chemistry. For several days he received a soft diet by mouth. The gastric contents were aspirated and replaced in the jejunostomy tube. His blood chemistry was kept near normal during the entire period. His urinary output was maintained at about 1,000 c.c. daily. His negative gastric balance was 2,000 to 3,000 c.c. daily. The gastric aspirations were replaced in the jejunostomy tube. He received a total of six transfusions.

On the thirtieth day after posterior gastroenterostomy, and twenty-two days after jejunostomy, he ran a positive balance for the first time. Thereafter, he improved rapidly. Barium by mouth showed an open gastroenterostomy stoma, with narrowing of the efferent loop of jejunum just distal to the stoma. His jejunostomy tube was taken out four days after a positive balance was obtained, and he was discharged from the hospital three days later, on Sept. 15, 1939, on a six-meal bland diet.

A repeat gastrointestinal series, on Feb. 9, 1940, showed barium passed through the gastroenterostomy without delay.

CASE 3.—R. C. (B. M. No. 223829), a 64-year-old native-born policeman, entered the hospital Nov. 7, 1939, complaining of persistent vomiting of five days' duration. He had had symptoms of epigastric distress relieved by soda twenty years before entry. Eleven years ago an x-ray diagnosis of duodenal ulcer was made. Nine years ago and one year ago he had recurrent attacks of pyloric obstruction. He began to vomit three weeks before entry and had been unable to retain any fluids for the past five days.

Physical examination was essentially negative except for obesity and dehydration. The blood count showed 4.29 R.B.C. and a white count of 10,900 with 84 per cent polymorphonuclears. Urine showed a specific gravity of 1.013 with 1 plus albumin. His blood chloride was 77.4 milliequivalents; the N.P.N., 100 mg. per cent; and protein, 7.6 per cent. Gastric analysis showed 48 units of free HCl and 73 one hour after test meal. A phenolsulphonphthalein test showed about 15 per cent excretion in two hours. Under the fluoroscope, marked pyloric obstruction was observed. No barium passed into the small bowel for two hours. At six hours a small quantity could be seen in the lower jejunum. He was completely obstructed and vomited 58 ounces soon after entry. He was given intravenous fluids and kept on nasal suction for six days. His N.P.N. dropped to 75 during this period. It seemed that no further improvement would occur, so a short-loop posterior gastroenterostomy without clamps was performed. It was noted that the omentum was extremely heavy and the mesocolon quite thick. There was an obstructing duodenal ulcer with marked dilatation of the stomach.

After operation, he ran a negative gastric balance regularly, averaging about 1,000 c.c. daily. He was given quantities of intravenous fluids so that his N.P.N. declined to 50, eight days after operation.

On the ninth postoperative day, because of persistent obstruction, the midline incision was reopened. The stomach had contracted quite remarkably. Two fingers could be passed from above into the anastomosis. No attempt was made to visualize the anastomosis from below, but a loop of jejunum was picked up about twelve inches distal to it. A No. 16 catheter was inserted and brought out in a subcostal position as a jejunostomy. Following the jejunostomy, he was given large amounts of fluid by this route. His N.P.N. continued to rise to 150. Obviously, he was failing to absorb all of the fluid given by jejunostomy. Intravenous saline solution was again employed. On the fifteenth day after jejunostomy, he developed a mild psychosis. During this period he was given chiefly milk, lime water, and vitamins through his jejunostomy. He was transfused a total of five times. On the sixteenth day after jejunostomy (i.e., the twenty-fifth day after posterior gastroenterostomy), his obstruction was relieved. This was proved by the fluoroscope, barium passing readily through the posterior gastroenterostomy.

At the end of this period of obstruction, he was in surprisingly good shape, although his N.P.N. was still 80. A repeat phenolsulphonphthalein test at this time showed less than 15 per cent excretion in two hours. He thereafter ran a positive gastric balance with no more vomiting. He was discharged from the hospital thirty-five days after the original operation.

Six months later the patient reported remarkable improvement. He had been entirely free of gastric symptoms and was working at his regular job.

CASE 4.—F. K. (B. M. No. 271724), a man, 51 years old, entered the hospital on Oct. 14, 1940, with an obstructing duodenal ulcer. He had been vomiting for several weeks and had lost about twenty pounds in weight. Barium studies showed almost complete pyloric retention. A posterior gastroenterostomy was done. He immediately began to run a negative gastric balance, varying from 2,000 to 4,000 c.c. daily. His N.P.N. rose to 50, while his serum protein remained at 6 per cent. Five days after operation, a jejunostomy was performed. Gastric aspirations and added milk and lime water were started almost at once through the jejunostomy tube. On the fourteenth postoperative day, his balance became positive and remained so. Four days later, barium was seen to pass slowly through the anastomosis. He was discharged from the hospital twenty-one days after his posterior gastroenterostomy, having lost very little time from the secondary operation and having gained considerable strength during that period.

CASE 5.—C. H. (B. M. No. 181231), a man, 66 years of age, had a known duodenal ulcer of nine years' duration. For the past six months he had been on a

diet and for one month had had very severe pain. X-ray showed 50 per cent retention in the stomach at the end of six hours and a duodenal ulcer on the posterior superior wall. At operation on Sept. 9, 1940, an active duodenal ulcer was found. A gastric resection was done with an anterior Hofmeister anastomosis. His immediate postoperative course was entirely uneventful. His nasal tube was removed on the fourth day. On the eighth postoperative day, he suddenly vomited 78 ounces. At that time, his N.P.N. was 13 mg. per cent and his protein 6.3 per cent. He then ran a negative gastric balance of approximately 2,000 c.c. daily. Six days afterwards a jejunostomy was done. Thereafter his serum protein remained above 6 per cent until he left the hospital. Fifty days after the resection, his gastric balance finally became positive and he was discharged from the hospital entirely relieved shortly thereafter.

CASE 6.—M. B. (M. G. H. No. 355463), a 24-year-old woman, on Aug. 12, 1936, had a Billroth I resection for a gastric ulcer. Obstruction began immediately after operation. On the fifteenth postoperative day, a jejunostomy was done. The obstruction was relieved on the thirty-second postoperative day and the patient discharged shortly thereafter.

CASE 7.—S. S. (B. M. No. 151669), a 70-year-old woman, had a resection of a carcinoma of the stomach with a posterior Polya anastomosis on Oct. 3, 1938. There was immediate marked postoperative obstruction. Five days after the resection, a jejunostomy was performed. Thirty-one days after the resection, relief of the obstruction finally occurred. The obstruction in this case appeared to be partially due to an abscess which drained through the lower end of her wound and to a serum protein which remained somewhat low throughout. She was finally discharged in good condition.

CASE 8.—H. B. (B. M. No. 73165), a 50-year-old man, had a Billroth I resection of the stomach for duodenal ulcer on Sept. 2, 1937. There was immediate postoperative obstruction. A week later, a jejunostomy was performed through a left subcostal incision. The anastomosis was found to be entirely normal. He developed wound sepsis, which drained satisfactorily. His obstruction was relieved on the twenty-sixth postoperative day. A year after discharge from the hospital, he had no gastric symptoms.

CASE 9.—S. B. (M. G. H. No. 153343), a 34-year-old man, entered with an obstructing duodenal ulcer. At laparotomy numerous adhesions about the common duct made a posterior gastroenterostomy advisable in preference to a resection. The gastric balance varied considerably from immediately after the operation but averaged about 1,000 c.c. on the negative side daily until thirteen days after operation when a jejunostomy was done. The negative balance then continued undiminished until thirty-one days after operation when the balance became positive and stayed there. The patient's N.P.N. and serum protein remained normal throughout.

CASE 10.—M. D. (B. M. No. 192291), a 74-year-old woman, entered the hospital on May 14, 1939. She had had six weeks of persistent vomiting. At operation, a large carcinoma was found adherent to the pancreas. A posterior gastroenterostomy was done. She began to vomit thick brown fluid almost immediately after operation. She ran a slightly positive gastric balance from the seventh to eleventh days but then it again became negative. Fifteen days after the posterior gastroenterostomy, the upper half of the wound was opened. There were numerous adhesions about the stomach. A Witzel jejunostomy was performed. A negative balance continued postoperatively until twelve days after jejunostomy when she began to take all feedings by mouth for the first time. She improved slowly and was finally discharged.

CASE 11.—J. A. (M. G. H. No. 237423). A gastric resection with a posterior Pólya anastomosis was done on this 65-year-old man on Oct. 25, 1940, for a carcinoma of the stomach. On the following day, he had a negative gastric balance of 1,500 c.c. This amount diminished and there was a slight positive balance from the fifth to tenth postoperative days. It then became negative again. On the fifteenth day a jejunostomy was performed. The gastric balance finally became positive twenty-five days after the resection and remained so thereafter.

CASE 12.—G. L. (M. G. H. No. 164699), a 59-year-old man, had a posterior Pólya resection for carcinoma of the stomach on Dec. 21, 1938. There was immediate postoperative obstruction that persisted until finally on the fifteenth postoperative day, a short incision was made under novocain beneath the left costal margin. A deliberate exploration was avoided. There were many adhesions observed about the anastomosis. The upper portion of normal bowel that was observed was used as a jejunostomy. Three days after this operation, it was noticed that jejunostomy feedings were immediately returned from the nasal tube. Dye introduced in the jejunostomy tube also appeared in the same way. The patient's N.P.N. remained at a normal level and his serum protein was 6.6 and 5.7 per cent at two determinations. He gradually lost ground and died on the twenty-ninth day after resection of bronchopneumonia. When jejunostomy was performed on this patient, it was done at too late a date and also was not done in the proper technical manner. This patient probably had definite stomal obstruction that persisted until practically no peristaltic activity was left in the small bowel. On the other hand, he may have had high jejunal obstruction from the beginning that was not discovered at the time of the exploration.

CASE 13.—W. I. (M. G. H. No. 163447), a 70-year-old man, was admitted to the hospital with carcinoma of the stomach and had a posterior Pólya anastomosis following a gastric resection on Dec. 14, 1938. There was a freely movable tumor and no evidence of metastatic disease. He ran a slight negative balance for four days and then this progressively increased until he was losing nearly 1,500 c.c. more by nasal tube than he was taking by mouth. Sixteen days after the first operation, a jejunostomy was done. The old incision was opened, many adhesions were found, and a Witzel type of jejunostomy was performed. His N.P.N. remained at a normal level. His protein was 5.5 and 6.4 per cent at two determinations. He lost ground steadily following his original operation and died two days after the jejunostomy. The cause of death as determined at autopsy was bilateral bronchopneumonia and pulmonary infarction. This was a patient of the older age group, who should have had a jejunostomy much earlier.

CASE 14.—C. C. (M. G. H. No. 16619), a 60-year-old man, had a posterior gastroenterostomy done for an obstructing duodenal ulcer on March 8, 1938. The transverse mesocolon was short and the procedure difficult. His preoperative N.P.N. was 87 and 117, while the serum protein was 5.2 per cent. He immediately began to run a large negative balance. However, with intravenous fluids, his N.P.N. came down to 32 and 35 mg. per cent and his protein rose to 6.4 and 6.7 per cent. He was finally explored because of persistent obstruction thirteen days after the original operation. Several adhesions were found about the distal loop and it was believed that they accounted for his obstruction; they were accordingly mobilized. No further procedure was done. He failed to improve so four days thereafter a jejunostomy was finally performed. He had been going steadily downhill and died three days after the jejunostomy with an N.P.N. of 102. Autopsy revealed no significant cause of death. This patient was uremic with a high N.P.N. before operation. His serious condition was not appreciated. Exploration was done too late on the thirteenth day and obviously should have included jejunostomy.

CASE 15.—J. L. (M. G. H. No. 29978), 60 years of age, was admitted for an obstructing duodenal ulcer and had a posterior gastroenterostomy performed on March 18, 1937. The operation was extremely difficult on account of a good deal of fat in the transverse mesocolon. He began to obstruct on the sixth postoperative day. He also developed a septic wound and partial wound separation. Finally after the obstruction failed to subside, twelve days after the original operation, he was again explored. There were numerous adhesions of the small bowel, especially about the stoma. An anterior gastroenterostomy was performed. This failed to function at all. After six days, another exploration was carried out. Numerous adhesions again were found. A tube was put in the upper jejunum. It was then found that fluid put in this jejunostomy tube came back through the stomach. Nine days after the original operation, another lower jejunostomy was made. This contributed nothing and the patient died two days later. The cause of death was plastic peritonitis. This was an old patient whose obstruction was complicated by other factors, such as a plastic peritonitis and wound separation. The obstruction was apparently not merely at the stoma but also at several other points in the jejunum.

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## SECTION OF THE SPINOTHALAMIC TRACT IN THE MEDULLA WITH OBSERVATIONS ON THE PATHWAY FOR PAIN\*

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SINCE Spiller (1905) first concluded that the pathway transmitting pain and temperature sensations resides in the anterolateral column, knowledge concerning the spinothalamic tract has advanced considerably. The observations of Collier and Buzzard (1903) upon the course of the tract through the cord to the ventral nucleus of the thalamus were elaborated in greater detail by Goldstein (1910). More recently Foerster and Gagel (1931) and Walker (1940) have traced the spinothalamic tract in Marchi preparations following anterolateral chordotomy.

A topical arrangement of fibers within the cord was suggested, among others, by Foerster and Gagel (1931), the fibers from the upper segments of the body lying more centrally and fibers from the lower segments occupying a more peripheral position in the spinothalamic tract. With minor modifications this arrangement has also been noted by Hyndman and van Epps (1939) and by Walker (1940). On the basis of animal experiments (LeGros Clark [1936], Walker [1938]) topical localization of fibers from various segments of the body has been demonstrated within the thalamus, and it is probable that a regular arrangement of fibers is present in the brain stem.

In the brain stem the spinothalamic tract is relatively superficial on the dorsolateral surface of the inferior olive. It then courses more deeply until the anterior border of the brachium pontis is reached; at this point it turns dorsally to occupy a superficial position once more. Dogliotti (1937, 1938) has reported cauterization of the tract in the mesencephalon by a supratentorial approach, resulting in analgesia of the contralateral half of the body. He has made no reference to the question of topical localization.

Recently one of us (H. G. S.) sectioned the spinothalamic tract at the junction of the middle and lower thirds of the inferior olive for relief of intractable pain. Prior to operation, careful examination revealed no diminution in or loss of any sensory modality. Sensory changes which occurred in different parts of the body during the operation were correlated with increasing depth of incision. In addition, observations upon partial section of the descending spinal tract of the trigeminal nerve were made.

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**CASE REPORT.**—The patient, a 30-year-old white woman, was referred to the neurosurgical service of the St. Louis City Hospital for relief of pain. Four years previously she first noticed a painful swelling of the left jaw. For two years she sought relief by morphine. In October, 1938, a mixed tumor was removed from the left submaxillary region. In April, 1939, a recurrence was apparent; the patient again resorted to morphine. She began to complain of pain in the chest; x-rays showed invasion of the left lung. There were several subsequent admissions until the end of May, 1939, when she was brought to the hospital after attempting suicide. On the advice of the neuropsychiatrists she was allowed to remain in the hospital to prevent self-destruction.

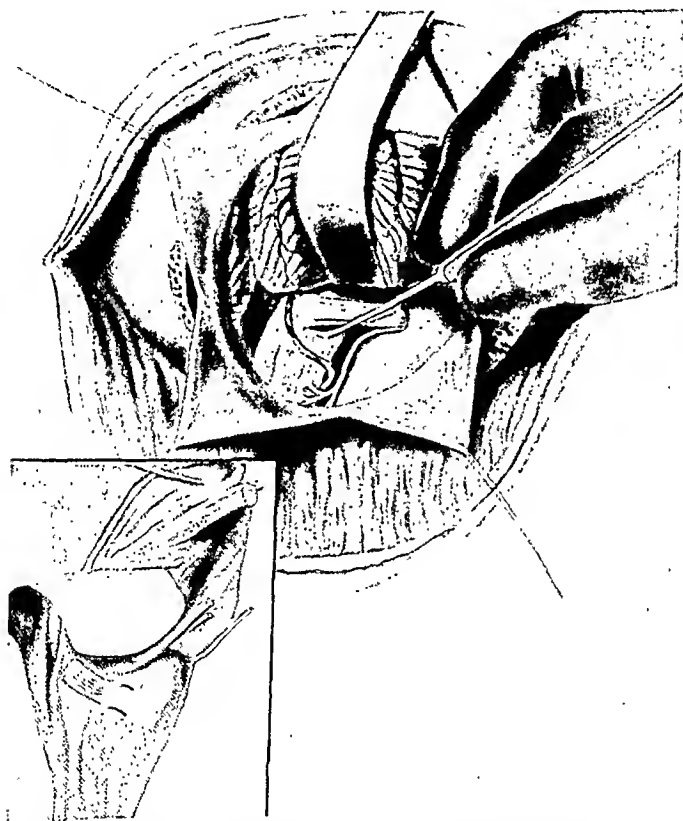
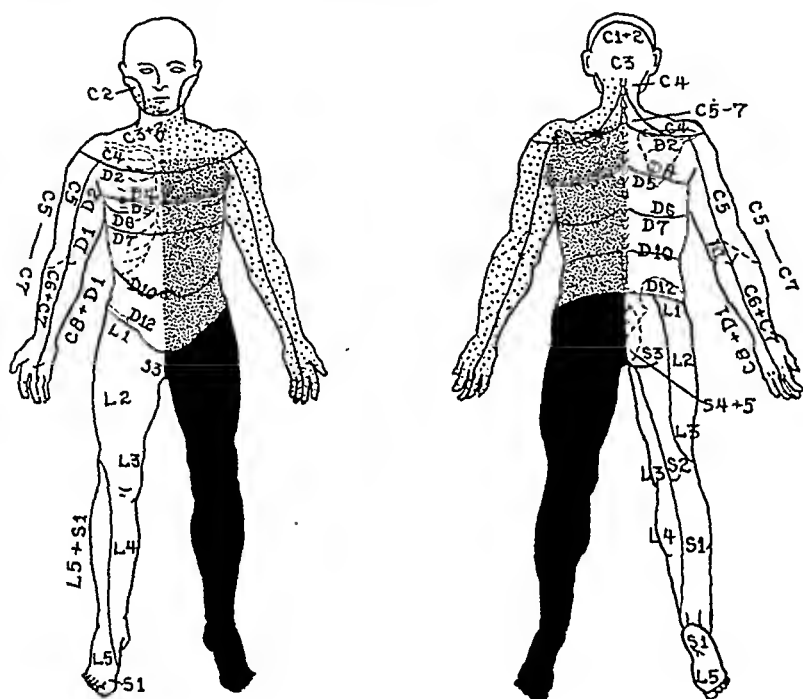


Fig. 1.—Showing exposure of right lateral wall of medulla for section of the spinothalamic tract. Knife point is directed between the roots of the vagus and the caudal portion of the inferior olive. Posterior inferior cerebellar artery is shown in its retracted position. Inset figure shows operative relations from a lateral view of a dissected brain stem, with the roots of the ninth and tenth nerves reflected back. The more rostral curved line indicates the site of incision which interrupted the descending trigeminal tract. The caudal line represents the point of entry of the incisions into the spinothalamic tract.

Pain in the left side of the neck, chest, and abdomen became worse, overshadowing the original mandibular pain. Steadily increasing doses of morphine were inadequate. There was no pain on the right side. In view of the distribution of the pain it was questionable whether even a high cervical section would be effective; in addition, since the left lung field was already practically functionless, the danger of traumatizing the fibers of the right phrenic had to be considered.

The possibilities for relief of pain and the danger of section of the spinothalamic tract at the level of the olive were fully explained to the patient. Despite the hazard involved, she begged for the operation. While waiting for the patient's scattered relatives to be found, her pain became progressively worse, until she was receiving 11 gr. of morphine daily with no more than transitory relief.

*Operation.*—(Jan. 27, 1940.) Avertin plus 3 gr. of morphine had no effect upon the patient's state of consciousness. Since we could rely upon her cooperation, it was decided to go ahead with local anesthesia. This made it possible to determine the effect of section during the operation.



■ Complete analgesia and loss of "tickling" sensation.  
Blunt touch preserved.

▨ Almost complete analgesia and loss of "tickling" sensation.

▤ Hypalgesia and diminished "tickling."

Fig. 2.—Illustrates the results of the postoperative sensory examination which was checked repeatedly.

A suboccipital skin incision was made (Fig. 1). The occipital bone was removed on the right side to just beyond the midline. After opening the dura and evacuating the spinal fluid in the cisterna magna, the right cerebellar tonsil was retracted upward. The right lateral wall of the medulla was exposed. The cervical roots of the spinal accessory nerve were identified, and then in succession the posterior inferior cerebellar artery, the bulbar portion of the spinal accessory,

the roots of the vagus, a small vein, and the glossopharyngeal nerve were encountered. The rostral part of the inferior olivary eminence was visualized just in front of and ventral to the ninth nerve. At this site, an incision about 3 mm. deep was made just ventral to the point of emergence of the glossopharyngeal nerve and paralleling its intrabulbar course. The patient complained of excruciating, lightning-like pain in the right jaw at the moment of incision. Examination showed no change in sensation over the body. From this, it was obvious that the descending trigeminal tract had been partially interrupted, and that the spinothalamic tract was not in the line of incision. Accordingly, the caudal portion of the inferior olive was exposed by gentle displacement of the posterior inferior cerebellar artery. An incision about 3 mm. in depth was then made

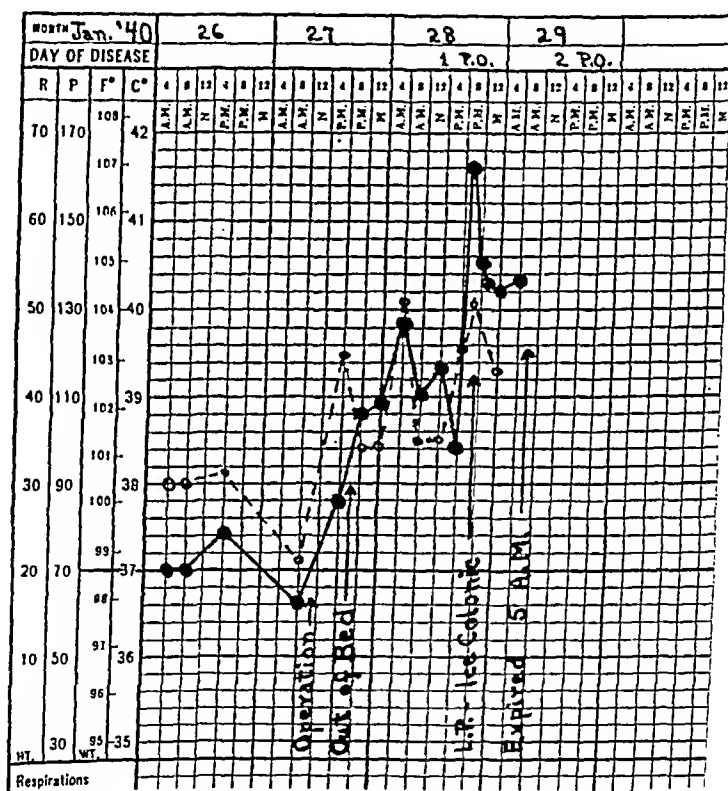


Fig. 3.—Chart representing the postoperative course.

between the undersurface of the vagus rootlets and the olive, these two structures serving as excellent landmarks. Examination showed loss of sensation to pinprick in the entire left lower extremity. In order to abolish pain completely a second incision was made at this same level, extending more medially to a depth of about 6 mm. It was designed to skirt the dorsal margin of the olive and so interrupt the remaining spinothalamic fibers which lie in this position (Goldstein [1910]). As this incision was progressively deepened, there resulted a corresponding progressive diminution of pain sensibility over the left side of the abdomen, chest, and upper extremity. The patient volunteered the information that the severe pain of the abdomen, chest, and neck was entirely gone. The only pain that persisted was confined to the left mandible. Trigeminal tractotomy

on the left side (by Sjöqvist's method [1938]) could have been performed through the same exposure. However, this was not thought justifiable since the residual pain was not very severe and could probably be relieved by alcohol injection of the third division later. The wound was closed in layers with silk. There was no respiratory embarrassment or difficulty in swallowing. The patient was sent back to the ward, grateful for relief of pain.

*Course.*—Fig. 2 shows the results of postoperative sensory examination which was checked repeatedly. There was complete analgesia and loss of "tickling" sensation over the entire lower extremity, with preservation of touch. There was almost complete analgesia over the trunk to the level of the clavicle. There was hypalgesia over the arm and neck up to the left mandible. In addition there was hypalgesia over the right mandible in an area corresponding to the distribution of the third division of the trigeminal nerve. The patient was completely free of pain except for the area of the left jaw. There was no motor weakness or ataxia. Sweating was equal on the two sides.

Fig. 3 represents the postoperative course. The patient's condition was excellent throughout the first day. At 7:00 P.M. on the evening after operation, she left her bed unassisted to look for a cigarette. The patient was rational and showed no apparent ill effects when she was visited at midnight. The next morning, temperature reached a peak of 103.8° F., but fell slowly to 101.2°, at 4:00 P.M. Her condition seemed to be excellent. Then there was a sudden spike to 107° with delirium. Lumber puncture was done; the fluid contained no more blood than is usually found after a craniotomy. Efforts to reduce the fever were only partially successful and the patient died two days after operation.

*Autopsy.*—A post-mortem examination was performed three hours after death by Dr. George Fraser of the Department of Pathology, St. Louis City Hospital. There was recurrence of mixed tumor in the submaxillary region. The left lung was almost solid with tumor; the right lung partly so. There was extensive metastatic involvement of the pleura, aortic nodes, diaphragm, liver, and the left kidney.

*Examination of the Brain (J. L. O'L.).*—There was no gross abnormality. The operative site was clean; there was no evidence of hemorrhage or edema. The sites of entry of the incisions were apparent. Thin slices made through the hemispheres, thalamus and hypothalamus showed no evidence of tumor invasion. The brain stem and attached remnants of the cerebellum were fixed in 15 per cent formalin. Later it was divided into blocks of convenient size, embedded in celloidin, and sectioned serially in a transverse plane at 40 microns. The sections were stained by the Kulschitzky modification of the Weigert method.

*Microscopic Examination.*—Serial Weigert sections of the brain stem from the level of the nucleus ruber to the rostral pole of the eighth nerve entry zone showed no evidence of secondary involvement of local lesions. In particular the fiber bundles of the lemniscus systems stained normally and equally on the two sides.

1. *Right Trigeminal Tract Lesion:* Just rostral to the known intramedullary course of the ninth nerve, an elongated lesion was observed in the dorsolateral area of the medulla. This lesion entered at the ventromedial angle of the restiform body and passed dorsally and somewhat medially to interrupt the ventrolateral part of the spinal trigeminal tract. At the point of entry the lesion was somewhat caudad to the cochlear division of the eighth nerve. It partially destroyed the spinal trigeminal tract at the level of the dorsal cochlear nucleus. (Figs. 4A and B.) The lesion was 3 mm. deep and extended over 56 40 micron sections (2.2 mm.). The lesion was too far lateral to interrupt the probable course of the spinothalamic tract at this level. It is possible that the olivocerebellar system was moderately damaged and that some secondary cochlear fibers directed toward the trapezoid decussation were interrupted, but no evidence of such involvement was apparent postoperatively.

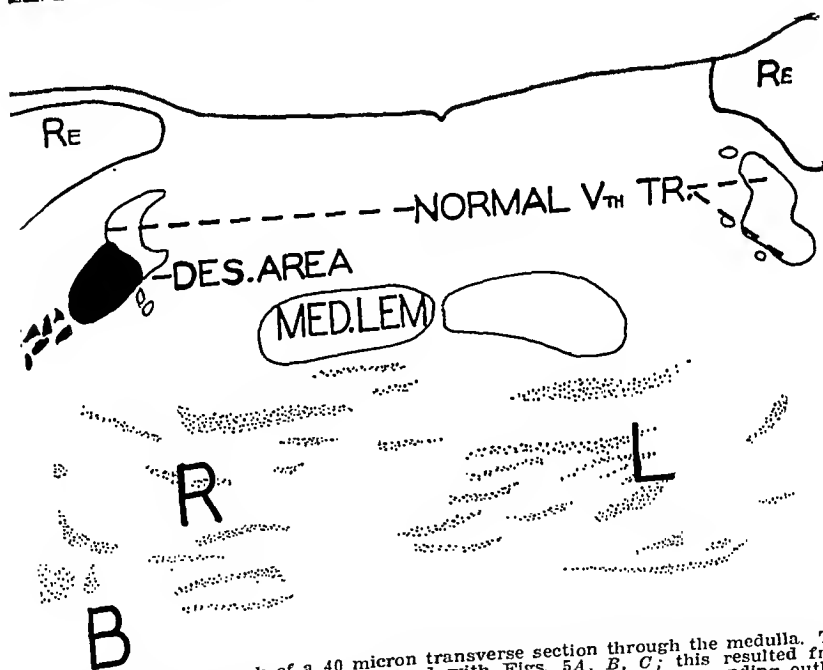


Fig. 4.—A, Photograph of a 40 micron transverse section through the medulla. The figure appears transposed when compared with Figs. 5A, B, C; this resulted from mounting sections from adjoining blocks in reverse order. B, Corresponding outline sketch; R, right; L, left; Re, restiform body; med. lem, medial lemniscus; des. area (solid black), interrupted fibers of right descending trigeminal tract, 5.5. diameters.

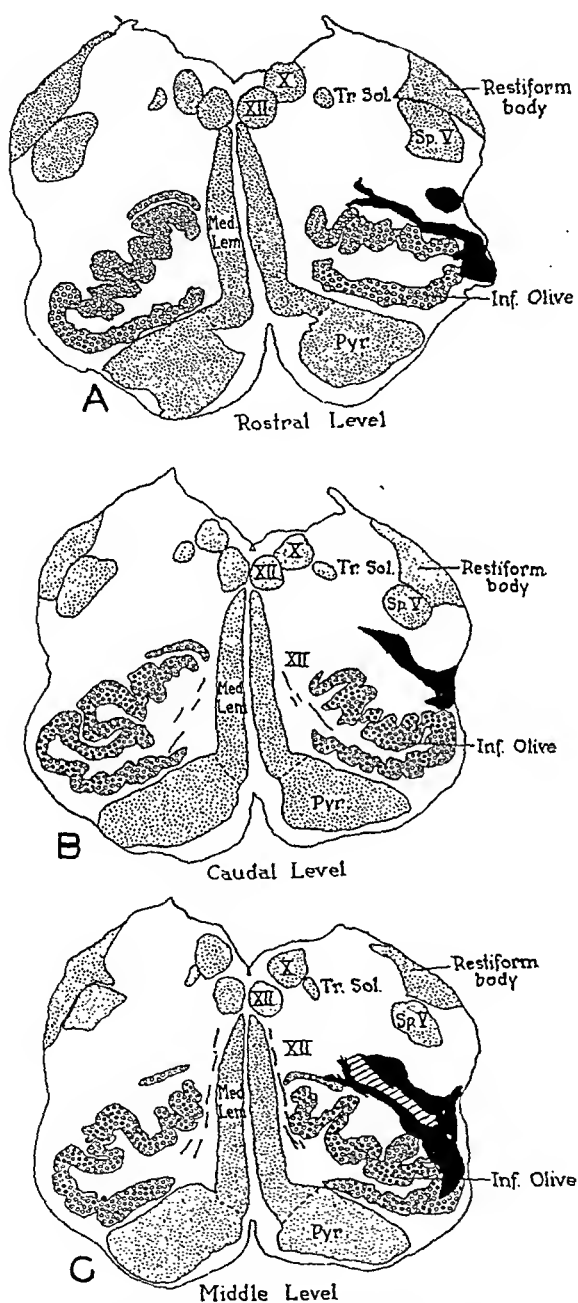


Fig. 5A, B, and C.—Outline drawings of transverse levels of the inferior olive, illustrating the situation and extent of the rostral (A) and caudal (B) lesions placed in the right spinothalamic tract. In C the total lesion is reconstructed upon a transverse section midway between A and B. XII, hypoglossal nucleus; X, dorsal motor nucleus of the vagus. *Tr. Sol.*, tractus solitarius; *Sp. V.*, descending trigeminal tract.

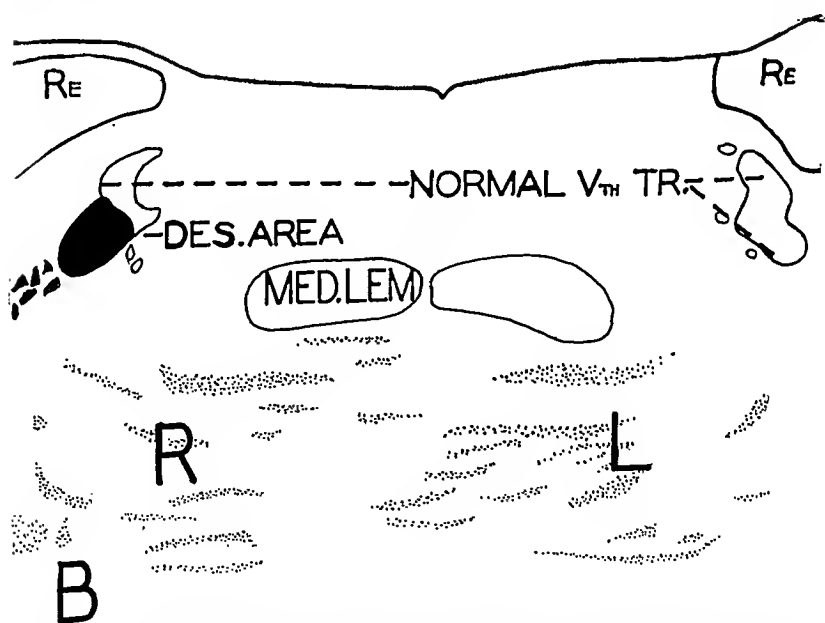


Fig. 4.—A, Photograph of a 40 micron transverse section through the medulla. The figure appears transposed when compared with Figs. 5A, B, C; this resulted from mounting sections from adjoining blocks in reverse order. B, Corresponding outline sketch: R, right; L, left; Re, restiform body; med. lem. medial lemniscus; des. area (solid black), interrupted fibers of right descending trigeminal tract, 5.5. diameters.

2. *Right Spinothalamic Tract Lesion:* Situated in the posterolateral sulcus overlying the lower third of the inferior olivary nucleus, a superficial lesion was detected. From this point of entry two stabs extended into the lateral area of the medulla, between the dorsolateral surface of the inferior olive and the ventrocaudal margin of the restiform body. The deeper and more rostrally situated of these stabs (Figs. 5*A* and 6*A*) shows a narrow tract which follows the dorsal margin of the inferior olivary nucleus. This lesion was 5.5 mm. deep and in its medial extent was separated by 3 mm. from the lateral margin of the medial lemniscus and by 4.4 mm. from the median raphe. Similar distances separated it from the dorsal motor nucleus of the vagus and the tractus solitarius.

The more caudal stab (Figs. 5*B* and 6*B*) was 4.3 mm. deep and was more dorsally situated, coursing just ventral to the spinal trigeminal tract but apparently not interrupting any of its fibers. Likewise its tip was well separated from the dorsal motor nucleus of the vagus and tractus solitarius.

The rostrocaudal extent of the entire spinothalamic tract lesion was confined to 45 40 micron sections (1.8 mm.). Fig. 5*C* reconstructs upon an outline drawing the whole area interrupted by the incision. Except for a focal softening upon the superolateral margin of the inferior olive there was a minimum of tissue damage at the margins of the lesion.

#### COMMENT

The observations on the sensory loss in this case may be considered in relation to the spinal trigeminal tract first and then the spinothalamic tract.

Davis and Haven (1933) have made careful observations on the deficit following experimental section of the sensory root of the trigeminal nerve in cats. Their experiments were microscopically controlled. They concluded that the posteroinferior portion of the root at its entrance into the pons carries the fibers of the ophthalmic division; in the spinal tract itself they found this arrangement is preserved so that the ophthalmic fibers lie in the ventral portion and the mandibular fibers lie in the dorsal portion. In man Sjöqvist (1938) has studied one patient who died several years after a differential section had been performed through the suboccipital approach. In this case the posterior inferior two-thirds of the root had been cut. No loss of sensation could be observed but the patient was free of second division pain for three years. In Kulshitzky sections Sjöqvist found degeneration in the dorsal part of the spinal trigeminal tract. He concluded that "the portion of the root which is cut at the Dandy operation corresponds to the dorsal (or superior) part of the tract and nucleus. This portion consequently must be formed by maxillomandibular fibers."

In the case that is presented in this paper there is evidence that the mandibular fibers of the trigeminal nerve were injured. At the moment of incision the patient complained of severe pain in the right (ipsilateral) jaw. Subsequent examinations demonstrated diminished pain sense in the distribution of the third division. Histologically, the lesion involved the ventrolateral portion of the spinal trigeminal tract. In this case, therefore, it appears that at the level of the dorsal cochlear nucleus the mandibular fibers are represented in the ventral rather than the dorsal area of the descending tract.

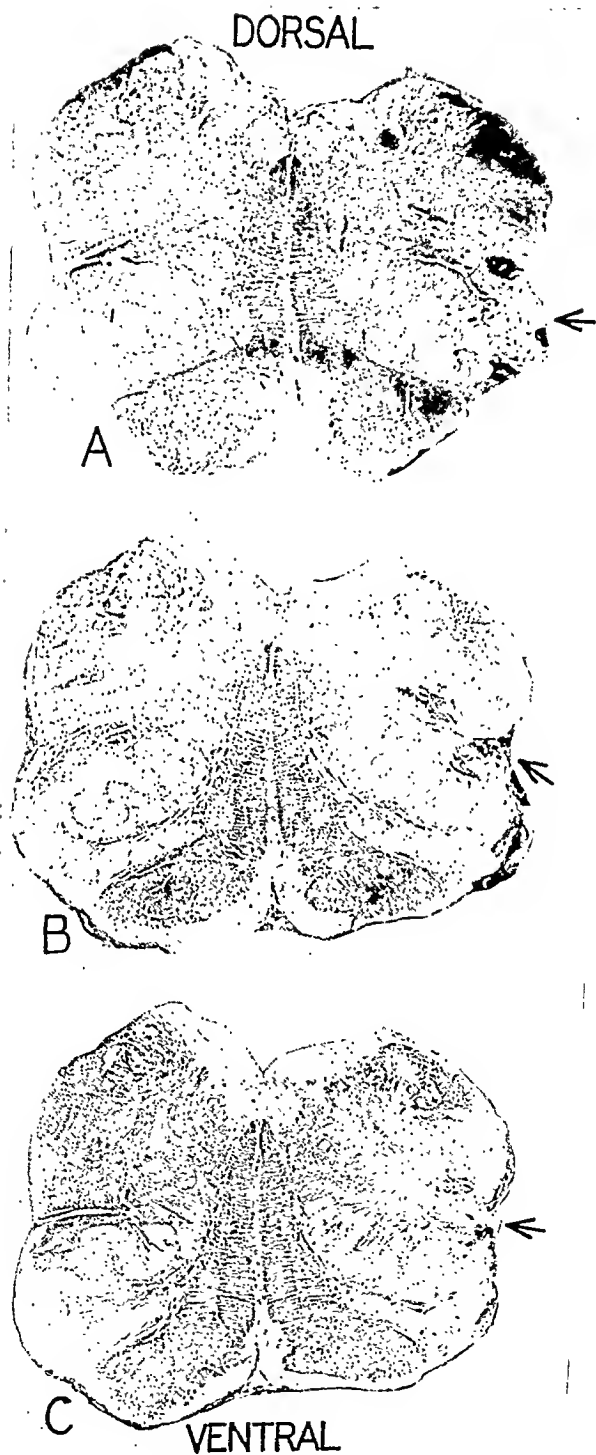


Fig. 6A, B, and C.—Photographs of transverse levels of the medulla corresponding to the outline drawings in Figs. 5, A, B, and C. Arrows indicate situation of lesion, 3.5 diameters.

death from carcinoma one month later. Details of this case will be reported in a subsequent communication.

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It is noteworthy that, although the patient complained of pain when the descending trigeminal tract was cut, there was no complaint when incisions were made into the spinothalamic tract. The explanation for this probably lies in the fact that in the former instance primary pathways were injured, while in the latter case secondary fibers were cut.

With regard to topical localization in the spinothalamic tract, the observations support the premise that in the brain stem, as in the cord, the fibers from the lower segments lie dorsolaterally, while those from the upper segments have a more ventromedial position. It was clear from examination made during the operation that the lower segments were affected by the dorsal incision into the tract and the upper segments were not involved until the second (ventral and medial) incision was made.

The association of loss of "tickling" sensation with loss of pain supports the view of Zotterman (1939) that these modalities are mediated by small fibers (less than 10 microns) which make up about 98 per cent of the fibers of the spinothalamic tract (Häggqvist [1936]). The observations in the present case offer no additional evidence concerning the position of the secondary tactile fibers in the brain stem.

#### SUMMARY

A case is reported in which section of the spinothalamic tract in the medulla was performed for relief of high, intractable pain. The operative technique is described. On the basis of sensory changes which resulted, it is concluded that a topical arrangement of fibers is present in the spinothalamic tract, with fibers from the lower dermatomes occupying a dorsolateral position and those from the upper segments lying ventromedially. A lesion involving the ventrolateral portion of the descending trigeminal tract was associated with disturbance of sensation in the distribution of the mandibular division of the fifth nerve.

Since this report was accepted for publication, Dr. James C. White (personal communication), of Boston, has confirmed the efficacy of the procedure, successfully relieving pain in a patient suffering from Raynaud's disease.

We have had additional experience in a second case of advanced malignant disease, in which the left spinothalamic tract was cut at the level of the inferior olive. This resulted in complete alleviation of pain in the right chest, shoulder, and axilla, caused by inoperable carcinoma of the breast with metastases. There was no involvement, indicating that the lesion extended into the neighboring descending tract of the trigeminal nerve, the nucleus ambiguus, medial lemniscus or vagal autonomic centers. We were able to confirm our previous opinion concerning topical localization of pain fibers within the spinothalamic tract in the brain stem. The patient was discharged from the Neurosurgical Service of the St. Louis City Hospital and was free of pain until her

The animals were sacrificed at from 8 to 142 days and a large piece of muscle or fascia containing the operated tissue was removed. The tissue was fixed in a modified Kaiserling solution and was later sectioned and examined microscopically for healing and type of union. Two animals showing slight wound infections were excluded from the series.



Fig. 1.—Showing area of union of severed striated muscle ( $\times 130$ ). Muscle from right back region, eighty-four days after operation.

#### RESULTS AND DISCUSSION

In the dog the skin wounds were almost healed eight days after suture; the union of muscle to muscle and of fascia to fascia was slightly less firm. Good healing occurred in muscle and in fascia in eleven days. Complete repair seemed to be present after sixteen days.

Microscopic study showed the healing to be the result of connective tissue growth and not through muscle cell regeneration (Fig. 1). We saw no evidence of typical or atypical muscle cell division in these experiments.

## WOUND HEALING

WITH ESPECIAL REFERENCE TO MUSCLE AND FASCIA REPAIR

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IT IS most generally held that, when muscle is severed and sutured, healing occurs by means of fibrous tissue elements from the epi-, peri-, and endomysium. Certain recent experimental studies on muscle repair indicate that muscle cells may regenerate (Forbus, 1926; Millar, 1934; Speidel, 1938; and Tauchi, 1934).

In 1923 Seelig and Chouké found that the suture of muscle to fascia failed to establish a firm union. Fascia sutured to fascia, on the other hand, united firmly. In the experiments here reported we have studied the healing of muscle and of fascia following incision such as surgical expediency would require. No attempt has been made to alter the physiology of the parts. The possible influence of various suture materials was also noted.

### METHODS

Seventy-two experiments were performed, sixty on twenty-one dogs and twelve on twelve rats. Thirty-three of the experiments on dogs involved suturing of muscle to muscle. All the experiments on rats concerned muscle-to-muscle union. In twenty-five experiments on dogs fascia was sutured to fascia. In two experiments the muscle-to-fascia union was restudied. Various muscles were employed in these experiments, such as the pectoralis major, external oblique, rectus abdominis, latissimus dorsi, trapezius, and others. The usual aseptic surgical technique was employed in the experiments on dogs but in the rats no special precautions were taken. Under anesthesia a particular muscle or fascia was exposed and freed of superficial areolar tissue. In most of the experiments the sutures were placed before the muscle was cut. Suturing was at right angles to the incisions. An attempt was made to secure close approximation of muscle edges without causing tension. The usual cut was transverse; in a few animals, however, oblique or longitudinal incisions were used. Since Howes (1933) reported that healing in some tissues seemed to be influenced by the variety of suture material, we used several different kinds, various sizes of black silk and plain and chromic catgut. After suturing the muscle, the overlying tissue and skin were closed, the latter by means of a subcuticular stitch. The wound was then sealed with collodion.

much firmer than the union between muscle and fascia. The union between muscle and fascia, even after complete removal of areolar tissue from both, was no more firm than that found by Seelig and Chouké.

In our experiments the kind of suture material employed did not appear to influence the nature or degree of union in either muscle or fascia.

#### SUMMARY

1. Healing of severed, striated muscle of dogs and rats occurs by fibrous connective tissue growth from the epi-, peri-, and endomysium, and not through regeneration of muscle cells.

2. Fascia unites readily to fascia, when closely approximated, by connective tissue growth.

3. The type of suture material employed (silk or catgut) did not appear to influence the degree or extent of union between fascia or muscle.

4. A firmer union developed between muscle and muscle and between fascia and fascia than Seelig and Chouké observed between muscle and fascia.

5. The union of muscle to muscle and fascia to fascia is complete eight to eleven days after suture.

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According to the experiments of Seelig and Chouké (1923) on dogs, normal muscle did not establish a firm union with fascia but fascia united readily with fascia. Koontz (1926) differed with these results. He believed that the union between muscle and fascia which he obtained was due to the removal of intervening areolar tissue. Hertzler (1927), commenting on this controversy, states: "Fibrous tissue alone can form a union. Fat bearing tissue prevents healing because fibrin bundles cannot form in the presence of fat. Muscle fibers will not heal; it is only the perimysium that can form a union. The ligature must be tied tight enough to traumatize the muscle so that a reaction is produced. It is this traumatic reaction which sets in action the fibrin formation that results in the formation of the fibrous tissue which makes the union." Hertzler believed that the different results reported by Seelig and Chouké and by Koontz could be explained on the ground that loose sutures were used by the former and tight sutures which traumatized the muscle were used by the latter. Seelig and Chouké felt that Koontz's own data showed that union between muscle and fascia occurs only between fascia and the fibrous elements of muscle.

According to MacCallum (1898), the muscle cells multiply and increase in bulk until the embryo is between 130 mm. and 170 mm. crown-rump length. After this stage, he writes: "The fibres now grow in length and thickness, but probably no longer increase in number. In embryos smaller than 170 mm. in length there is a regular increase in the number of fibres found in a cross-section. After this, however, the number remains approximately constant." As in normal growth, our experiments did not show the formation of any new muscle cells. The repair took place by means of the fibrous connective tissue formed between the cut ends of the muscle fibers. Recently both preserved and living fascia lata has been used in the repair of hernias (Haas, 1931; and Hodgkins, 1930). According to Haas (1931), the union affected by these depends mainly on ingrowth of endo- and perimysium: "The muscle cells themselves appeared to be transformed into elements of fibrous tissue."

Our findings differ from those of Forbus (1926) in rabbits and from those of Speidel (1938) in tadpoles. The differences may be attributed in part to the techniques employed. In our experiments the muscle fibers were severed; in those of Forbus the muscle was injured by injection into it of irritant substances. This damaged the muscle fiber, but its sarcolemma remained intact. Speidel observed complete regeneration of the muscles of the tadpole's tail after various kinds of injuries. He mentions cutting and bruising but omits the details concerning regeneration after these procedures. Further Speidel studied larval amphibian forms while our work is based on incisional trauma in adult mammals.

Correlating our results with those of Seelig and Chouké (1923), the union between muscle and muscle and between fascia and fascia is

into component parts. This agglutination has led observers to consider the possibility that postoperative wound separation in the absence of frank infection is due to catgut allergy. Some support is lent to this hypothesis by consideration of the source of the blood-tinged fluid that stains the dressing before separation actually occurs. Edema of the tissues plus excessive fluid formation indicates that the inflammatory reaction incidental to healing has exceeded normal bounds and, in this respect, simulates an allergic reaction. The chief advantages of suture are that complete replacement of prolapsed intestines is effected without delay and that, in lesser degrees of separation, suture will prevent extension of the process and further eventration. Other advantages are that the period of hospitalization is less and that there is more likelihood of healing without hernia formation than when nonoperative treatment has been employed. The chief disadvantage of suturing is that the procedure subjects an already sick patient to an operation of some magnitude. Certainly only relatively few patients whose laparotomy wounds break open are in condition to stand the shock of a general anesthetic and even a minimal operative procedure. Each patient will stand just so much operative trauma, and disaster is certain to follow when this limit is exceeded. A study of the mortality rate following secondary closure in wound disruption indicates that this threshold has been overstepped on many occasions. Patients who would not be considered good risks for the second stage of a divided operation are subjected to secondary closure, simply because an emergency exists. Immediate operation has long been demanded for surgical emergencies, but gradually the concept has arisen that preparation of the patient for operation is of equal, if not greater, importance than the operation itself. Thus no longer is the dehydrated, shocked, or anemic patient submitted to operation, but rather surgery is deferred until blood and fluid levels are restored. But if this is true of most present-day surgical emergencies, it does not hold for the serious emergency of wound disruption, for most patients with this complication are submitted to operation without delay. In consideration of the course of action to be followed in any surgical emergency, it is well to bear in mind that the decision not to operate is just as important as the decision to operate. The former, however, requires more fortitude on the part of the surgeon, for, while all observers consider themselves capable of passing judgment on occasions when failure to operate might have been the cause of a fatality, few give any consideration to the role played by untimely operations.

Immediate suture of wound disruption should be carried out only in the best-risk patients. If there is any question regarding the ability of the patient to stand the operation, nonoperative methods of treatment are clearly indicated. It is questionable if inhalation anesthetics should ever be administered to these patients, because the straining so often

## THE MANAGEMENT OF POSTOPERATIVE WOUND SEPARATION

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ONE of the most serious complications of laparotomy is the breaking open of the wound. The occurrence of this condition fortunately is low, for, even if allowance is made for unrecorded cases, published statistics indicate that approximately only 1 per cent of abdominal wounds disrupt. But if the frequency is low, the mortality is high, varying, according to the literature,<sup>1, 4</sup> from 25 to 50 per cent. Perhaps a 35 per cent mortality is a fair estimate. While it must be admitted that the cause of death in many instances is due to underlying pathologic conditions, at the same time, the method of management currently in vogue deserves attention.

### GENERAL MEASURES

Regardless of the course of treatment about to be pursued, the first requisite is to allay the patient's fear by administration of barbiturates. Seconal gr.  $1\frac{1}{2}$  to gr. 3 by mouth, if it can be retained, or sodium phenobarbital gr.  $1\frac{1}{2}$  by hypodermic, if there is nausea, removes apprehension. There is seldom a complaint of pain in the presence of wound disruption. On the contrary, many patients admit to relief of distress when the wound margins separate. However, morphine sulfate, gr.  $\frac{1}{4}$ , by hypodermic should be given to prepare the patient for a general anesthetic, to augment local anesthetic, or to relieve the distress of manipulation when nonoperative procedures are employed.

The next most important step in treatment is to arrange for a blood transfusion as soon as possible, for it should not be overlooked that these patients are seriously ill. Apart from the correction of hypoproteinemia,<sup>8</sup> if this condition exists, blood is the best supportive and restorative medium at the surgeon's disposal. It is also essential to control vomiting, when present, by means of the indwelling duodenal tube, and to restore the fluid level, when indicated, by the intravenous administration of 5 per cent glucose.

### IMMEDIATE SUTURE

The teaching and practice of most surgical centers is to advise immediate resuture of the wound when disruption occurs. In most instances, closure of the wound is accomplished by through-and-through suture of silver wire,<sup>6, 7</sup> steel wire, silkworm gut, or braided silk. Layer suture is seldom possible, because the usual finding is that the layers of the abdominal wall are so well agglutinated that they cannot be separated

ings moistened in saline may now be applied over the intestine. It is well to use at least three thicknesses of gauze dressing so that the superficial layers can absorb the serous discharge which always occurs. The gauze dressing lying next to the intestine should not be removed or replaced until it has loosened itself from scrota, a process that will require four or five days. Flamed one-inch adhesive strips are prepared by a nurse and applied by an assistant, who removes his gloves. The strips should be long enough to grasp the full width of the abdominal wall. They should be applied first over the center of the protrusion; one then works both up and down to the extremities of the wound. Firm pressure should be applied, and effort should be made to reduce the eversion and coapt the wound margins. This will rarely be possible, but with succeeding daily dressings, the edges of the wound can be brought together gradually. In certain instances, injection of 0.5 per cent novocain into the wound margins will aid these manipulations. It is important to change the adhesive daily because there is always some loosening due to the slipping of the strips or further reduction of the protrusion. When applying fresh adhesive strips, the same aseptic precautions as for the first dressing must be exercised, and reopening of the wound must be prevented by removing and replacing the strips one at a time. Absorbent gauze pads are placed over the adhesive strapping, and further support is supplied by a firm abdominal border.

If it is possible to bring the wound edge together at once, healing will occur just as rapidly and just as soundly as when sutures have been employed. But when coaptation is effected gradually, healing will be slower and incisional hernia is more certain to ensue than if closure had been obtained by sutures.

#### AFTERTREATMENT

Aftertreatment, regardless of the method of closure, should begin with a blood transfusion. Ileus is of such frequent occurrence that the indwelling duodenal catheter should be used on all patients with wound disruption, since the earlier treatment is begun, the more likely it is to be effective. In our experience, intestinal obstruction has been due more often to inflammatory than to mechanical ileus. The former yields to hot stupes and continuous duodenal suction drainage, but the latter is a definite indication for operative intervention.

Mechanical obstruction is, of course, the one definite contraindication to nonoperative treatment. However, since the exact nature of the obstruction is not always apparent, there is nothing lost by conservative treatment, since, even if operation is definitely indicated later, the supportive measures already instituted will enable the patient to better withstand surgical intervention. Vitamin C,<sup>5</sup> because of its value in

associated with induction is likely to increase the amount of separation and prolapse. Furthermore, since coughing is the chief predisposing factor in wound separation, an anesthetic agent which is not irritating to the respiratory system should be chosen. Spinal anesthesia fulfills the requirement, but increasing experience has taught that spinal is not the anesthetic of choice for poor-risk patients. These objections, then, limit the selection to local anesthesia. Subcostal block plus infiltration of the wound margin and extraperitoneal tissues with 0.5 per cent novocain solution skillfully and patiently administered will permit reduction of the prolapse and suture of the wound margins without undue discomfort to the patient. Preliminary medication with seconal gr. III by mouth and morphia gr.  $\frac{1}{4}$  by hypodermic will diminish both the psychic and actual distress of the patient. If it is not feasible to move the patient to the operating room in his bed, he should be operated upon in his room. The practice of lifting patients out of their beds onto a stretcher, taking them to the operating room, and then transferring them to an operating table is to be deplored, because these movements, no matter how carefully controlled, increase the amount of prolapse and add to the shock of an already sick patient. Layer suture is rarely possible because of edema and agglutination of the tissues. In the vast majority of cases, closure is best effected by through-and-through sutures. These are put in at intervals of 3 cm. and should be placed about 5 cm. from the wound margins. Care should be exercised when closing an infraumbilical incision not to include the deep epigastric artery in the bite of the suture, lest the vessel be eroded from pressure of the suture material and serious hemorrhage ensue. Silver wire still holds the field as the choice of suture material, although it is possible that the newer plastic suture materials may in time supplant it. The great advantage over silkworm gut is that wire does not tend to cut through the tissues because of its larger diameter. Braided silk is flexible and easier to handle, but stitch abscesses almost invariably form around the skin openings.

#### CLOSURE BY ADHESIVE STRAPPING

Adequate sedation, using opium derivatives and barbiturates, is the first requisite. Absolute asepsis is maintained only when the surgeon is prepared as for any other surgical procedure, a preparation which should include masking. An assistant removes the protective dressing and prepares the skin margins of the wound by cleaning with ether to dissolve the fat, so that the adhesive will stick. Care must be exercised when applying skin antiseptic not to allow it to come in contact with the delicate intestinal serosa. If evisceration has occurred in an infected field, or has been unrecognized for several hours, it may be well to lavage the protruded viscera with warm normal saline solution. Gauze dress-

## CONCLUSION

A plea is entered for the wider adoption of conservative treatment in abdominal wound disruption. The high mortality following secondary closure is caused in part by a desire to treat the existing emergency rather than the patient.

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promoting wound healing, should be given in dosages of 300 mg. per day because smaller doses are ineffectual. Hypoproteinemia is combatted by repeated small blood transfusions, but if the blood concentration is at or near normal and the serum protein and serum globulin are below normal, blood plasma should be administered. The recent work done with lyophile serum<sup>8</sup> and intravenous amino acids<sup>2</sup> perhaps opens up a new field of therapy, but we have had no experience with administration of these substances.

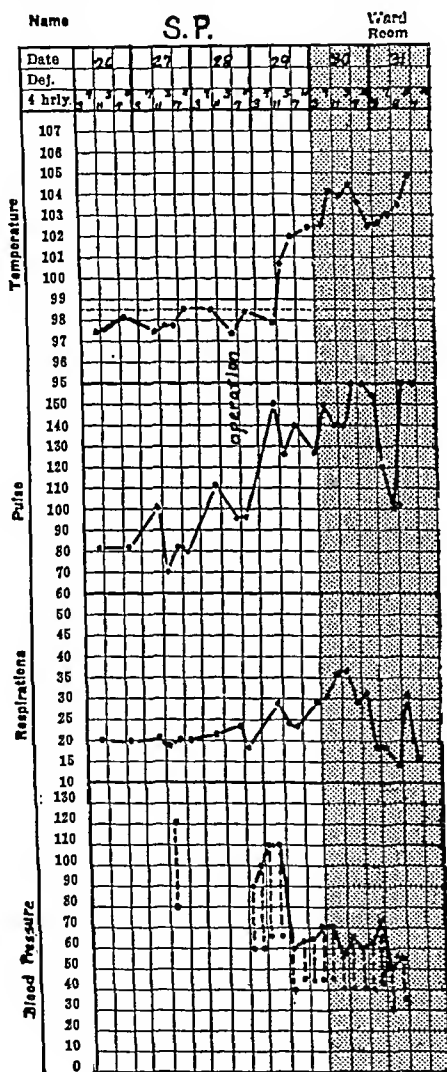
#### COMMENT

In 1936 I reviewed all the recorded cases of wound disruption at the Henry Ford Hospital up to and including the year 1935.<sup>3</sup> The mortality rate of 34 per cent, while appalling, was not out of line with other published reports. A detailed study of the fatal cases yielded the thought-provoking observation that 70 per cent of the patients who died did so within twenty-four hours of being subjected to operation for secondary closure. The inference then must be that, in certain cases at least, the operation itself was a determining factor in the fatal issue. This does not mean that all the patients would have recovered if the disrupted wound had not been operated upon, for many of them were doomed because of the condition that required surgical interference in the first place and from other complications. However, it does suggest that alternative methods of management of wound disruption should receive serious consideration.

Since the beginning of 1936 we have treated at the Henry Ford Hospital twenty-seven cases of wound disruption occurring in 4,153 laparotomies, an incidence of only 0.65 per cent. The mortality rate for this small series was 37.3 per cent and compares favorably with 34 per cent for our former series; but what is more significant is the evidence in favor of nonoperative treatment. Seven of the sixteen patients whose wounds were resutured died, a mortality of 43 per cent, but only three of the eleven patients whose wounds were treated by adhesive strapping died, a mortality of only 27.3 per cent.

It will always be difficult to introduce statistical evidence in favor of nonoperative measures because the tendency is to restrict their use to the more seriously ill group of patients where the mortality is certain to be high with any form of treatment. However, the evidence in favor of the nonoperative treatment of wound disruption in our own cases has resulted in a reversal of our former practice of operating upon all patients as soon as the diagnosis was established. Secondary suture has gradually been abandoned until, in the past two years, all instances of wound disruption occurring on the general surgical service have been treated by packing and adhesive strapping—a course that in our hands has yielded excellent results.

CASE 2.—S. C., a 39-year-old woman, was admitted to the hospital for surgical collapse therapy, the diagnosis being bilateral pulmonary tuberculosis and left tuberculous empyema. The patient had developed tuberculous empyema during pneumothorax treatments; the fluid contained no organism except the tubercle bacillus. At physical examination the patient's general condition was found to be fairly good, and no extrathoracic abnormality of importance was present. The cardiovascular status was excellent. The red cell count was 4.8 million; hemoglobin, 85 per cent. The white cell count was 9,600, and the smear showed 56



per cent polymorphonuclears, 35 per cent lymphocytes, 8 per cent monocytes, and 1 per cent eosinophiles. The urine was negative. Chest x-ray study showed the right lung clear and the left atelectatic beneath pyopneumothorax.

On March 24 left upper five-rib thoracoplasty was performed without incident under nitrous oxide-oxygen-ether anesthesia. The patient stood the operation well and was in good condition at its conclusion. Next day, thirty hours after

## POSTOPERATIVE SHOCK DUE TO HEMOLYTIC STREPTOCOCCUS WOUND INFECTION

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THE essential features of secondary or traumatic shock may be produced by various noxious forces, and usually such harmful influences are present in combination. The state of "vascular failure"<sup>1</sup> accompanying reduction in circulating blood volume, hemoconcentration, and lowered systolic blood pressure, when appearing soon after operation, usually signifies to the clinician disturbances of homeostasis by a conspiracy of harmful agents. It is the purpose of this report, however, to draw attention to the syndrome of postoperative shock depending on a particular cause, fulminating infection of the wound with hemolytic streptococcus. Early recognition of the true nature of the condition is of lifesaving importance, and specific treatment of the infection rather than symptomatic treatment of shock is urgently indicated.

CASE 1.—S. P., a 37-year-old woman, was admitted to the hospital for surgical collapse therapy for chronic pulmonary tuberculosis with cavitation. Nine months previously the patient had undergone upper thoracoplasty on the right in two stages with good results. She had shown much improvement, with gain in weight and strength and diminution in cough and sputum. She was readmitted for treatment of cavitation at the left apex. Her general physical condition was excellent, and there was no extrathoracic abnormality of significance. The heart appeared normal; the blood pressure was 120/80. There was a mild coryza, in view of which the operation was postponed for three weeks. The red cell count was 4.5 million, the hemoglobin 80 per cent. The urine contained albumin, but was otherwise negative.

On Jan. 28 left upper thoracoplasty with removal of three ribs was performed under nitrous oxide-oxygen-ether anesthesia without difficulty, there being no untoward reaction. Next day, twenty-four hours after operation, the patient went into a state of collapse, with systolic blood pressure of 60, cold clammy extremities, slight cyanosis, and rapid small pulse. Diagnoses considered by the house staff were hemorrhage into the wound, pericardial effusion, pneumothorax, or pleural effusion. The patient was mentally alert and appeared to have no particular discomfort. A chest film was made, but gave no help in diagnosis. Blood transfusion and saline solution infusions were given.

On Jan. 30 the patient's condition was unimproved, the state of shock having continued unrelieved. The rectal temperature was 104°; the white cell count was 36,000, and the operative wound now came under suspicion. Externally the wound looked innocent, but the fluid aspirated was found on smear to contain numerous gram-positive cocci, and culture yielded a heavy growth of hemolytic streptococci. Further transfusions were given, but the peripheral vascular collapse continued, and the patient died Jan. 31, three days after operation. There was no autopsy.

tuberculosis, left encapsulated tuberculous empyema, hemolytic streptococcus infection in the thoracoplasty wound, and hemolytic streptococcus bacteremia.

CASE 3.—M. C., a 62-year-old woman, was admitted to the hospital for surgical treatment of carcinoma of the left breast, noted eight weeks previously. Admission had been postponed for two weeks on account of a severe upper respiratory infection. The patient's general condition was excellent on admission. The nasopharynx and

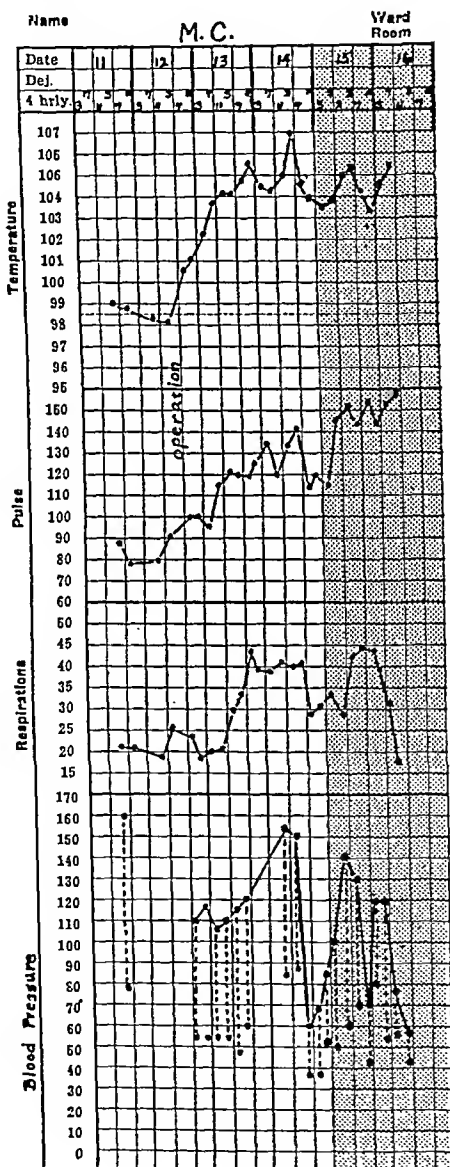


Fig. 3.

bronchi showed no evidence of persistent respiratory infection, and chest x-ray study was negative. The blood pressure was 160/76 and the heart seemed normal. There was a mass retracting the nipple of the left breast, but the skin did not appear to be directly involved and there was no ulceration or dermatitis. No involvement of

operation, a sudden alarming drop in the patient's blood pressure was noted. The blood pressure was 70/40; the extremities were cold and clammy; the pulse was rapid and feeble. Diagnoses considered were hemorrhage into the wound and tension pneumothorax. Aspiration of the wound and left pleural cavity excluded these possibilities, but the fluid was not examined bacteriologically, as infection of the wound was not suspected. On March 26 the patient's condition was worse and the vascular collapse persisted despite blood transfusions. The steadily rising temperature

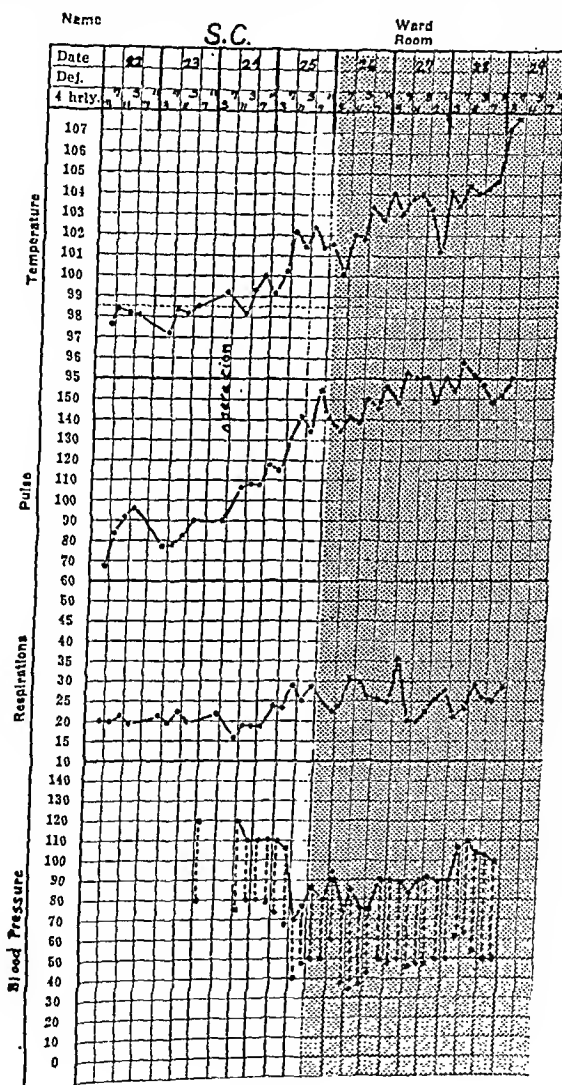


Fig. 2.

and pulse rate and the presence of induration where the skin was penetrated during chest tap the day before suggested wound infection. The wound was opened and serosanguineous fluid containing hemolytic streptococci in abundance was evacuated. The patient's condition steadily failed, however, and death in hyperpyrexia occurred five days after operation. Autopsy showed bilateral pulmonary

agreed with the tentative diagnosis of acute adrenal insufficiency and suggested also the possibility of pulmonary embolism and auricular fibrillation. Digitalis was administered, and an electrocardiogram showed auricular tachycardia with varying degree of auriculoventricular heart block. A cardiological consultant, however, favored a diagnosis of pulmonary embolism. Oxygen therapy was instituted. Seventy-two hours after operation blood cultures taken twenty-four hours after operation were reported as showing heavy growth of hemolytic streptococci.

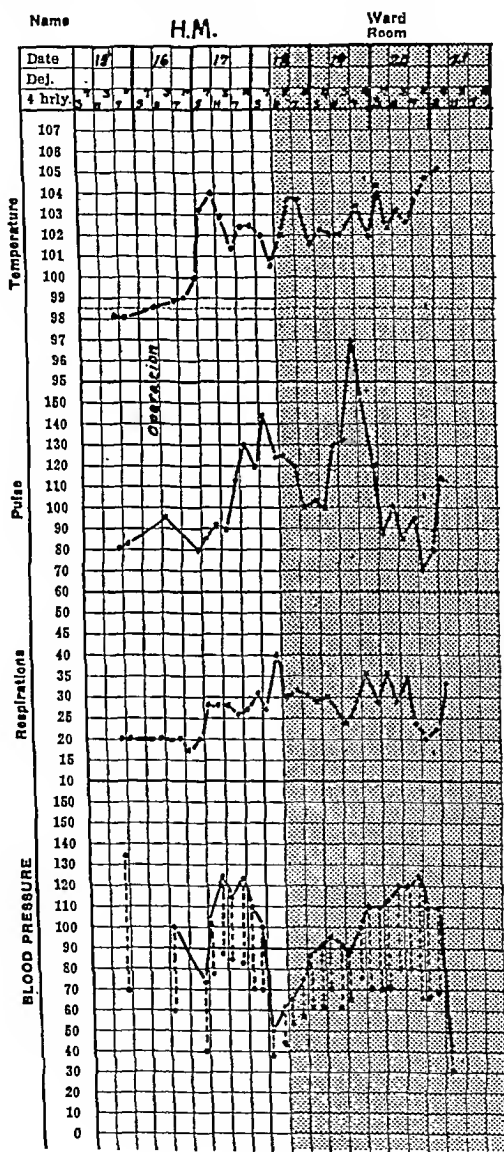


Fig. 4.

Another consultant interpreted the picture as classical of peripheral endophlebitis with septic infarction of the lungs and began sulfanilamide and antibacterial antibody therapy, but on the following day the patient died, five days after operation.

the axillary nodes could be made out. The temperature was normal; the white cell count was 10,100, with normal differential values, and the red count was 4.9 million. The urine was normal.

On March 12 left radical mastectomy was performed under ether anesthesia and the wound was closed without drainage. There was considerable blood loss during the operation, and at the end of the operation the patient's blood pressure had declined from 160/80 to 80/50, and there was other evidence of mild shock. The response to infusion of solution of 10 per cent glucose and 0.9 per cent sodium chloride was rapid, however, and the same evening the patient's condition was good, though the blood pressure was slow in returning to the preoperative level. Next day, twenty-four hours after operation, the rectal temperature was 104° and the pulse rate was 120. The wound was examined and appeared satisfactory. Indefinite signs at the base of the right lung were interpreted as indicative of consolidation and explanatory of the fever. On March 14, forty-eight hours after operation, the patient suddenly developed the signs of severe shock, and in three hours the blood pressure dropped from 150/86 to 60/36. The extremities were cold, wet, and grayish. The mental reactions were interesting, the patient being alert, quickly responsive, and somewhat exhilarated. The wound was opened and 2 or 3 ounces of dark reddish fluid containing numerous streptococci was evacuated. The wound was packed open with gauze moistened in physiologic salt solution; blood transfusion was given and administration of prontosil parenterally was begun. Blood cultures were positive for hemolytic streptococci, and cultures of fluid from a bleb on the leg gave abundant growth of the same organism. The patient's condition steadily failed; the hyperpyrexia continued and she became delirious and died four days after operation. Autopsy showed hemolytic streptococcus infection of radical mastectomy wound with bacteremia and early bilateral bronchopneumonia.

CASE 4.—H. M., a 48-year-old woman, was admitted to the hospital for diagnosis and treatment of persistent dull pain in the lower abdomen of two years' duration. Seventeen years previously right transperitoneal nephrectomy had been performed for hypernephroma. Seven years before admission excessive uterine bleeding had been treated by production of artificial menopause by irradiation. Her recent health had been good except for chronic lower abdominal ache, worse in the right lower quadrant. Her general physical condition was found excellent; there was no pulmonary or cardiovascular abnormality, and the blood pressure was 135/70. Laboratory studies, abdominal scout films, and intravenous pyelography were negative.

On Dec. 16 exploratory laparotomy, appendectomy, and excision of the lower two-thirds of the previous laparotomy scar were performed under ether anesthesia. There were adhesions beneath the laparotomy scar and the appendix was fibrotic and thickened, though not acutely inflamed. The stump of the appendix was carbolized but not buried. Next morning the patient's condition seemed alarming. Her rectal temperature was elevated, but her extremities were cold and clammy and the blood pressure was 74/40. She seemed to have no pain and was mentally clear. The attending surgeon was unable to account for the state of shock, but ordered a blood transfusion to be done. The white cell count was 26,500; the red cell count was 4.2 million, and in the smear many young polymorphonuclear forms were seen. The patient's vascular collapse was somewhat benefited by blood transfusion and saline solution infusions, but her condition continued to be precarious. Thirty-six hours after operation an internist in consultation made a tentative diagnosis of acute adrenal insufficiency from hemorrhage into the adrenals. Cortical extract was administered, and a second blood transfusion was given the patient.

On Dec. 18, forty-eight hours after operation, the patient suddenly developed signs of severe shock, the blood pressure falling to 50/38. A second consultant

such an explanation must remain conjectural. All the members of the operating teams were free from upper respiratory infections, and wore standard folded gauze masks which covered mouth and nose. The inadequacy of the usual surgical oronasal mask is notorious, however.<sup>7-9</sup> A practicable method insuring the complete protection of a large wound from air-borne oronasal organisms during a long operation can hardly be said to exist, but progress toward this goal has recently been made.<sup>10, 11</sup> Two of the above cases occurred the same winter. Other factors, such as personnel of the operating teams, preparation of the field of operation, and location of the operating rooms were variable.

These cases were dealt with before chemotherapy and immunotransfusion had become the effective weapons they now are in treating virulent infection due to the hemolytic streptococcus. In Cases 3 and 4 tardy use of prontosil and sulfanilamide in insufficient dosage was made. It can hardly be doubted that recognition of the wound infection immediately after the telltale signs of shock appear in such cases would make it possible to treat them with some success. A fatal delay may result from treating the signs of shock rather than the underlying cause. Immediate aspiration of the wound with examination of the stained smear should lead to immediate diagnosis and proper treatment.

#### CONCLUSION

Four cases are presented which illustrate the syndrome of postoperative shock due to fulminating infection of the field of operation with hemolytic streptococci. In these cases there was a delay of more than twenty-four hours after the onset of shock before the presence of wound infection was suspected. The urgent need for immediate recognition of the infection in such cases, in order to permit specific treatment by methods of chemotherapy and immunotransfusion, is stressed.

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The autopsy showed hemolytic streptococcus peritonitis and bacteremia, acute poriphlebitis and lymphangitis of the left leg, and acute serofibrinous pleuritis. The adrenal glands were normal.

*Discussion.*—The charts of rectal temperature, rate of pulse and respiration, and systolic and diastolic blood pressure, determined at three-hour intervals, are shown for each case (Figs. 1-4). Heavy black ink is used in the charts up to the point of onset of shock, while cross-hatching is used thereafter, to bring out the contrast between the appearance of the chart at the time shock set in and terminally.

These cases have in common the sudden onset of shock within forty-eight hours after extensive operations on previously uninfected tissues. In each instance the infecting organism was the hemolytic streptococcus and the outcome was fatal within five days. The patients were under close observation and the manifestations of shock appeared with startling abruptness. Such evidence of infection as fever and leucocytosis was not distinct enough at the time vascular collapse developed to suggest the true diagnosis to the medical attendants, and it was only twenty-four hours or more afterward that wound infection was suspected. In the meantime the state of shock was variously attributed to hemorrhage, pulmonary embolism, acute adrenal insufficiency, pneumonia, auricular tachycardia and heart block, multiple septic pulmonary infarcts, tension pneumothorax, pericardial tamponade, or to a combination of such factors. All such etiological possibilities were excluded by the clinical and autopsy findings, leaving no doubt in these cases that shock and death were due to fulminating streptococcus infection.

It is a well-known fact that the onset of shock may mark the progress of overwhelming infections, such as pneumonia,<sup>2</sup> diphtheria,<sup>3</sup> and gas gangrene,<sup>4</sup> though, as Warfield points out,<sup>5</sup> the failure of circulation is often erroneously ascribed to cardiac weakness. The essential feature is probably reduction in venous return and cardiac output dependent on widening of the capillary bed and on plasma loss into the inflamed areas.<sup>6</sup> The importance of the factor of increase in size of the capillary bed is evidenced in the cases being reported above by the rapidity with which the circulatory collapse developed. Whether such capillary paralysis results from the sudden release into the general circulation of large amounts of bacteria or bacterial toxins, which act directly against the capillary wall, is an interesting question of considerable prognostic import.

Regarding the source of the infection in these cases, there is no conclusive evidence. It may be of significance, however, that the infections all occurred during the winter months. From this, probable origin in the nasopharynxes of those in the operating room may be inferred, but in the absence of studies which might have established the presence of the same strain of hemolytic streptococcus in the nasopharynx of a member of the operating team and in the patient's wound

TABLE I

PROTHROMBIN RESPONSE IN VARIOUS DISEASES DURING ORAL ADMINISTRATION OF 1 MG. METHYL NAPHTHOQUINONE IN CORN OIL AND 0.5 GM. DEOXYCHOLIC ACID DAILY

PATIENT	AGE	DIAGNOSIS	DATE	PLASMA BILIRUBIN MG./100 C.C.	PLASMA PROTHROMBIN %
M.M.	54	Common duct stone	11/ 9/39	8.8	48.6
			11/11/39	2.6	76.7
J.C.	37	Common duct stone	3/ 4/40	17.0	44.6
			3/ 8/40		86.2
F.N.	55	Hepatic carcinoma	2/27/40	24.3	52.8
			3/ 4/40	24.0	76.0
B.L.	46	Toxic hepatitis, liver failure	3/ 4/40	27.0	46.3
			3/ 7/40	33.0	42.6
A.H.	54	Portal cirrhosis, liver failure	3/16/40	9.5	43.0
			3/20/40		40.4
G.S.	30	Chronic ulcerative colitis	2/ 3/40	Normal	64.2
			2/ 5/40		68.7
			2/ 7/40		77.9
I.G.	18	Disseminated lupus	2/ 3/40	Normal	32.2
			2/ 5/40		54.7
			2/ 7/40		63.2
M.L.	35	Steatorrhea, regional ileitis	10/ 3/39	Normal	40.0
			10/10/39		95.3

prothrombin concentration also occurred in the 2 patients having initial values between 50 and 75 per cent.

Twelve patients were given orally the dipropionyl derivative of methyl naphthoquinone in corn oil with deoxycholic acid, as shown in Table II. The 1 patient in the group whose initial plasma prothrombin value was below 50 per cent showed rapid improvement. Nine patients had initial concentrations between 50 and 75 per cent and 7 showed improvement under treatment.

As shown in Table III, of the 14 patients receiving parenterally the sodium bisulfite derivative of methyl naphthoquinone, 5 had initial plasma prothrombin concentrations of less than 50 per cent. Of these 5 patients 4 showed improvement within forty-eight hours after a single injection of the vitamin K material. Nine patients had initial values between 50 and 75 per cent, and 7 showed satisfactory response to the treatment.

In considering these results more broadly, of the 20 patients treated by the oral administration of methyl naphthoquinone or its dipropionyl derivative plus deoxycholic acid, 5 failed to show improvement in prothrombin concentration in three to six days of treatment. Four of these 5 patients had severe intrinsic liver disease and died of liver failure. Of the 14 patients given vitamin K substance subcutaneously, as shown in Table III, 2 made no prothrombin response and 1 of these patients died of liver failure. In 1 patient dying of cirrhosis of the liver and liver failure, the plasma prothrombin concentration remained below 50 per cent despite the oral administration of deoxycholic acid in conjunction with methyl naphthoquinone and large doses of crude vitamin K extracted from alfalfa meal, and despite the subcutaneous injection of the sodium

## ORAL AND PARENTERAL USE OF SYNTHETIC VITAMIN K-ACTIVE SUBSTANCES IN HYPOPROTHROMBINEMIA

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ON THE basis of recent laboratory and clinical investigation, the vitamin K potency of certain synthetic naphthoquinones may be regarded as tentatively established.<sup>1-5</sup> Questions which require further study concern the dosage of the naphthoquinones, their toxicity, the need for giving bile salts with them, the choice of oral or parenteral administration, and the duration and uniformity of prothrombin response.

In the present study of thirty patients with hypoprothrombinemia, plasma prothrombin was determined by the method of Warner, Brinkhous, and Smith<sup>6</sup> as slightly modified.<sup>7</sup> The normal value by this method ranges from 90 to 110 per cent, while the zone of dangerous tendency to spontaneous bleeding is below 40 per cent. The 2-methyl-1,4-naphthoquinone and the 2-methyl-1,4-dipropionyl-naphthohydroquinone used were kindly supplied by A. Black of E. R. Squibb & Sons. The water-soluble sodium bisulfite derivative of 2-methyl-1,4-naphthoquinone was synthesized by M. B. Moore and F. J. Kirchmeyer of Abbott Laboratories. The latter substance is probably the sodium salt of the 3-sulfonic acid of 2-methyl-1,4-naphthoquinone. The deoxycholic acid used was furnished by Riedel de-Haen, Inc. As determined by biological assay on the chick, 1.8 mg. of the sodium bisulfite derivative orally administered is equivalent to 1 mg. of 2-methyl-1,4-naphthoquinone, or to 2,500 Peirce-Dann units and 62,500 Dam units.<sup>8</sup> The dipropionyl derivative also is about one-half as active as 2-methyl-1,4-naphthoquinone.<sup>9</sup> The assumption is probably justifiable that the vitamin K potency of these substances is as great given parenterally as orally.

On the basis of treatment the patients may be divided into three groups: those who took methyl naphthoquinone and deoxycholic acid orally; those who took the dipropionyl derivative and deoxycholic acid by mouth; and those who were treated by subcutaneous administration of the sodium bisulfite derivative of methyl naphthoquinone. As shown in Table I, 8 patients were studied while taking daily by mouth 1 mg. of methyl naphthoquinone in corn oil and 0.5 Gm. of deoxycholic acid. The therapy lasted from two to seven days. Six of the 8 patients had initial plasma prothrombin values below 50 per cent, and in 4 of these the response to treatment was excellent. Satisfactory improvement in

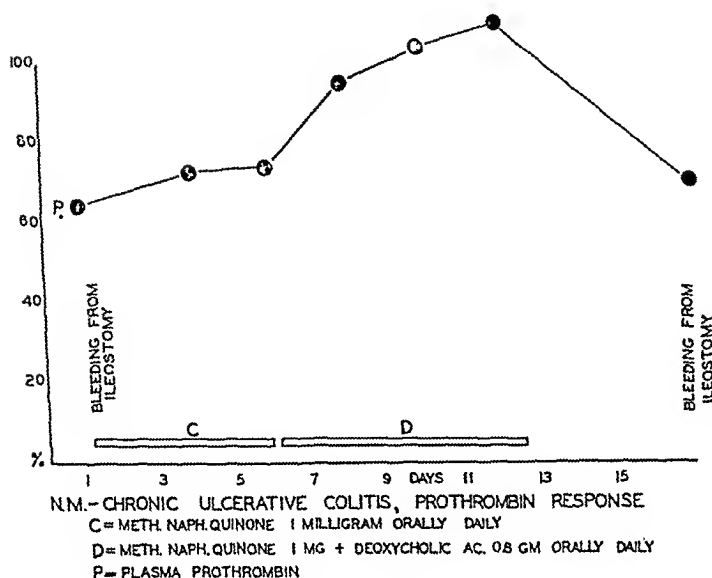
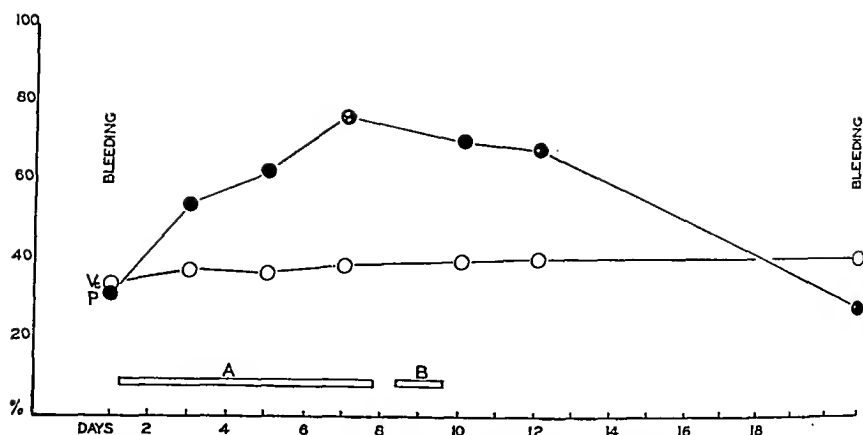


Chart 2.

TABLE III

PROTHROMBIN RESPONSE IN VARIOUS DISEASES AFTER SUBCUTANEOUS ADMINISTRATION OF SODIUM BISULFITE DERIVATIVE OF METHYL NAPHTHOQUINONE

PATIENT	AGE	DIAGNOSIS	DATE	PLASMA BILIRUBIN MG./100 C.C.	PLASMA PROTHROMBIN %	DOSAGE
E. E.	39	Common duct stone	12/ 1/39	1.9	63.4	1.8 mg. s.c.
			12/ 2/39	1.9	95.9	12/1/39
J. Z.	50	Common duct stone	1/27/40	7.2	71.4	1.8 mg. s.c.
			1/31/40		75.0	1/30/40
J. B.	57	Carcinoma of pancreas	12/ 9/39	26.5	11.5	1.8 mg. s.c.
			12/11/39	24.5	92.6	12/9/39
C. B.	58	Toxic hepatitis, liver failure	12/ 1/39	16.9	54.1	1.8 mg. s.c.
			12/ 2/39	21.0	92.2	12/1/39
W. W.	60	Carcinoma of common duct	12/27/39	20.2	51.1	1.8 mg. s.c.
			12/28/39		107.2	12/27/39
M. L.	51	Common duct stone	12/16/39	22.5	68.5	1.8 mg. s.c.
			12/21/39	22.2	90.8	12/20/39
W. B.	53	Toxic hepatitis	2/ 2/40	23.0	73.0	3.7 mg. s.c.
			2/ 3/40	22.0	101.3	2/2/40
R. G.	52	Portal cirrhosis, ascites	3/16/40	14.0	37.0	3.7 mg. s.c.
			3/18/40		38.4	3/17/40
E. D.	60	Common duct stone	3/16/40	Normal	59.2	3.7 mg. s.c.
			3/18/40		76.5	3/17/40
H. C.	34	Portal cirrhosis, hematemesis	4/ 2/40	Normal	48.3	3.7 mg. s.c.
			4/ 4/40		58.9	4/2/40
C. D.	41	Portal cirrhosis, liver failure	4/ 2/40	22.2	42.0	3.7 mg. s.c.
			4/ 4/40		61.5	4/2/40
V. D.	23	Perinephric abscess	2/ 6/40	Normal	53.1	3.7 mg. s.c.
			2/ 7/40		62.7	2/6/40
R. M.	24	Periarteritis nodosa	2/12/40	Normal	34.9	3.7 mg. s.c.
			2/14/40		92.3	2/13/40
H. G.	17	Ileal fistula, intestinal obstruction	4/ 5/40	Normal	57.2	3.7 mg. s.c.
			4/ 6/40		69.5	4/5/40



IG.- DISSEMINATED LUPUS. DURATION OF PROTHROMBIN RESPONSE

A = METH. NAPH. QUINONE 1 MG + DEOXYCHOLIC AC. 0.8 GM ORALLY DAILY

B = SULFONIC DERIVATIVE 3.7MG S.C. DAILY

Vc = RED CELL HEMATOCRIT IN PERCENT

P = PLASMA PROTHROMBIN IN PERCENT

Chart 1.

bisulfite derivative and the intravenous administration of methyl naphthoquinone.

Improvement in prothrombin concentration cannot be expected to persist after cessation of vitamin K therapy, unless the underlying

TABLE II

PROTHROMBIN RESPONSE IN VARIOUS DISEASES DURING DAILY ORAL ADMINISTRATION OF 2 MG. METHYL DIPROPIONYL NAPHTHOHYDROQUINONE PLUS 0.5 GM. DEOXYCHOLIC ACID

PATIENT	AGE	DIAGNOSIS	DATE	PLASMA BILIRUBIN MG./100 C.C.	PLASMA PROTHROMBIN %
N.M.	27	Chronic ulcerative colitis	10/21/39	Normal	65.1
			10/28/39		95.0
B.O.	69	Common duct stone	10/26/39	3.9	87.1
			10/28/39	2.2	96.0
C.H.	54	Biliary cirrhosis	10/11/39	9.4	56.4
			10/20/39		85.8
E.E.	39	Common duct stone	11/22/39	6.0	69.7
			11/25/39	6.0	96.1
K.T.	55	Toxic hepatitis, liver failure	10/18/39	20.0	53.1
			10/20/39	22.0	57.2
W.B.	53	Toxic hepatitis	1/18/40	24.5	51.0
			1/24/40	26.8	96.1
J.H.	77	Carcinoma of common duct	1/24/40	24.6	38.1
			1/29/40	19.0	92.7
A.M.	79	Common duct stone	11/27/39	7.4	72.4
			12/ 1/39	4.9	91.9
C.B.	58	Toxic hepatitis, liver failure	11/16/39	25.6	62.7
			11/20/39	31.6	69.5
			11/22/39	29.2	60.2
W.W.	60	Carcinoma of common duct	12/ 4/39	22.7	59.1
			12/11/39	3.7	81.1
W.B.	36	Hepatic carcinoma	10/26/39	22.2	55.1
			10/28/39	28.2	90.0
R.W.	58	Common duct stone	10/26/39	1.3	78.5
			10/30/39	1.0	78.9

tration was moderately satisfactory after large doses of sodium bisulfite derivative of methyl naphthoquinone were given subcutaneously. Only small benefit was obtained from the oral administration of methyl naphthoquinone, plus deoxycholic acid, and from the intravenous injection of methyl naphthoquinone. Up to 20 mg. of methyl naphthoquinone, dissolved in 300 c.c. of 0.9 per cent NaCl solution, was given to this patient by vein without untoward effects. The data from this case suggest the futility of giving large doses of methyl naphthoquinone if the usual dose of 1 to 4 mg. per day is ineffective.

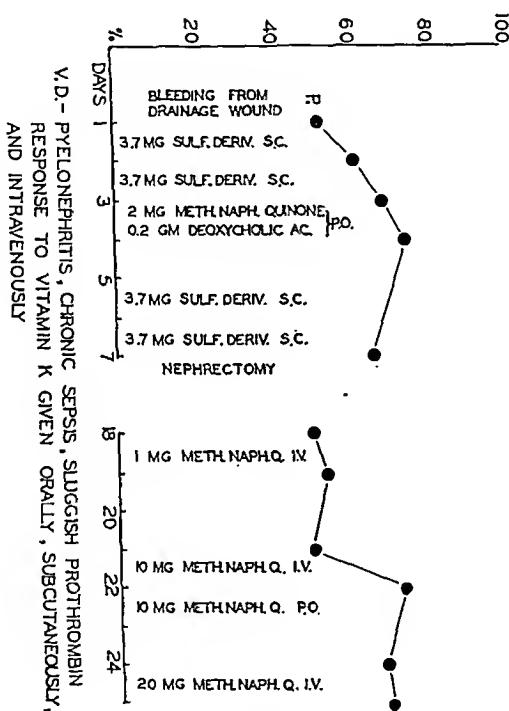


Chart 4.

## COMMENT

Sweeping conclusions are not to be drawn in this study, but certain impressions stand out with distinctness. It is clear that prothrombin-lack and an abnormal bleeding tendency may occur in various conditions in which there is no reason to suspect the presence of severe liver disease. Disseminated lupus, steatorrhea, chronic ulcerative colitis, chronic sepsis, and periarteritis nodosa were among the conditions illustrative of this point in the present study. The occurrence of prothrombin deficiency in such varied conditions points up the fact that the fundamental nature of the disturbance is still unknown.

An interesting and puzzling occasional clinical finding is prothrombin deficiency refractory to vitamin K therapy. Failure to respond to

disease has been corrected. This point is brought out by the data in Chart 1, from the study of a patient with disseminated lupus and pathologic bleeding. This patient took methyl naphthoquinone and deoxycholic acid orally during Period A, while during Period B the sodium bisulfite derivative was given parenterally. Bleeding from the nose and mouth and into the skin was relieved, only to recur when the prothrombin value declined to 30 per cent after cessation of treatment.

The beneficial effects of giving deoxycholic with methyl naphthoquinone are suggested in Chart 2, the data of which were obtained in studying prothrombin changes in an extremely sick patient with chronic ulcerative colitis. This patient was not jaundiced, hence it is of special interest that deoxycholic acid had to be taken with the methyl naphthoquinone orally to restore the prothrombin value to normal. With relief of hypoprothrombinemia, there was definite reduction in bleeding from the ileostomy.

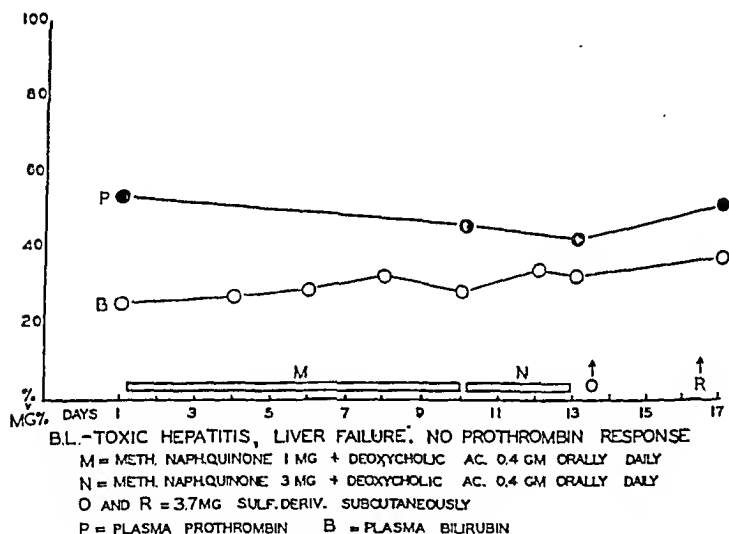


Chart 3.

Prothrombin deficiency may be resistant to treatment in severe hepatic insufficiency, as shown in Chart 3, from the study of a patient with progressive liver failure. The plasma prothrombin values in per cent and plasma bilirubin in milligrams per 100 c.c. are indicated. Neither the oral nor parenteral administration of potent vitamin K-active substances led to improvement in the plasma prothrombin value. Nevertheless, the prothrombin concentration failed to reach extremely low levels, and at no time was there evidence of pathologic bleeding.

Data shown in Chart 4 from the study of a patient with chronic sepsis, prothrombin deficiency, and bleeding from a surgical drainage wound illustrate sluggishness of prothrombin response to intensive vitamin K therapy. The improvement in plasma prothrombin concentration

treatment may sometimes be attributable to liver damage of such severity that hepatic synthesis of prothrombin is no longer maintained, even in the presence of the precursor substances. In other cases, however, particularly in chronic sepsis, there may be no evidence on which to incriminate the liver. If one supposes that prothrombin consists of a globulin molecule linked with a vitamin K prosthetic group, then prothrombin deficiency might conceivably depend on inadequate formation of the protein molecule.

Deoxycholic acid and bile salts seem to increase the effectiveness of methyl naphthoquinone when taken orally, even in the absence of jaundice and known intrahepatic disease. Whether this denotes deficient excretion of bile salts and normal pigment excretion in such cases, or whether the synthetic processes in the liver are favorably influenced by ingestion of cholic acid derivatives is a matter for speculation. The point is of considerable importance in choosing between oral and parenteral methods of giving vitamin K. There seems to be no conclusive evidence to cover the question, but theoretically the administration of bile salts in the presence of biliary obstruction may be harmful to renal, hepatic, and other tissues. It is probably wise to give only small amounts of bile salts for the absorption of fat-soluble K-active substances in obstructive jaundice, or else to give preparations suitable for parenteral use and not give bile salts.

The brevity of the prothrombin response after a single dose of vitamin K is worthy of comment. Evidently there is little storage of vitamin K in the body, and sustained effects are not to be expected from a single massive dose if the underlying disease persists. Daily small doses of from 1 to 4 mg. of methyl naphthoquinone, or the equivalent, would seem to be better therapy than occasional larger doses. Such a conclusion is supported by previously published observations on the lability of plasma prothrombin and the need for determining the value frequently in handling cases of obstructive jaundice.<sup>10</sup>

#### SUMMARY

In a study of 30 patients with miscellaneous diseases and prothrombin deficiency, the following impressions were obtained:

1. 2-methyl-1,4-naphthoquinone, its dipropionyl derivative, and its sodium bisulfite derivative have satisfactory vitamin K-potency taken orally or parenterally in dosage of 1 to 4 mg. daily.

2. No evidence of toxicity was seen in giving as much as 20 mg. of 2-methyl-1,4-naphthoquinone intravenously in one dose.

3. The prothrombin response to treatment appears within twenty-four hours and lasts less than a week after vitamin K therapy is ended. The daily administration of vitamin K is desirable in treating hypoprothrombinemia.

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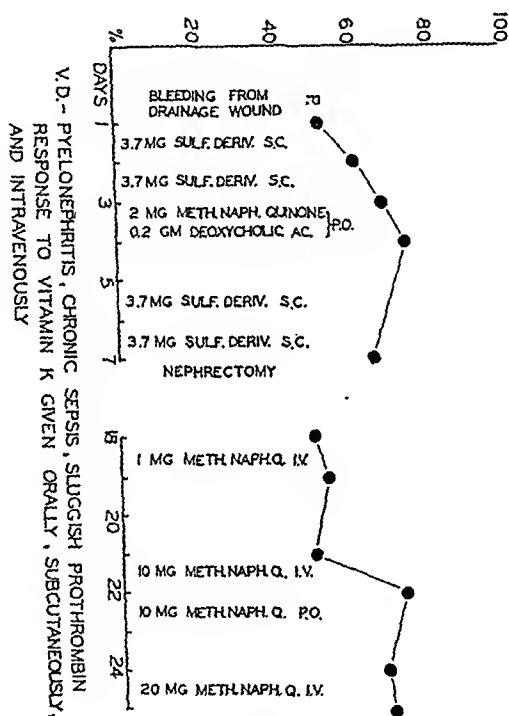


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An interesting and puzzling occasional clinical finding is prothrombin deficiency refractory to vitamin K therapy. Failure to respond to

treatment may sometimes be attributable to liver damage of such severity that hepatic synthesis of prothrombin is no longer maintained, even in the presence of the precursor substances. In other cases, however, particularly in chronic sepsis, there may be no evidence on which to incriminate the liver. If one supposes that prothrombin consists of a globulin molecule linked with a vitamin K prosthetic group, then prothrombin deficiency might conceivably depend on inadequate formation of the protein molecule.

Deoxycholic acid and bile salts seem to increase the effectiveness of methyl naphthoquinone when taken orally, even in the absence of jaundice and known intrahepatic disease. Whether this denotes deficient excretion of bile salts and normal pigment excretion in such cases, or whether the synthetic processes in the liver are favorably influenced by ingestion of cholic acid derivatives is a matter for speculation. The point is of considerable importance in choosing between oral and parenteral methods of giving vitamin K. There seems to be no conclusive evidence to cover the question, but theoretically the administration of bile salts in the presence of biliary obstruction may be harmful to renal, hepatic, and other tissues. It is probably wise to give only small amounts of bile salts for the absorption of fat-soluble K-active substances in obstructive jaundice, or else to give preparations suitable for parenteral use and not give bile salts.

The brevity of the prothrombin response after a single dose of vitamin K is worthy of comment. Evidently there is little storage of vitamin K in the body, and sustained effects are not to be expected from a single massive dose if the underlying disease persists. Daily small doses of from 1 to 4 mg. of methyl naphthoquinone, or the equivalent, would seem to be better therapy than occasional larger doses. Such a conclusion is supported by previously published observations on the lability of plasma prothrombin and the need for determining the value frequently in handling cases of obstructive jaundice.<sup>10</sup>

#### SUMMARY

In a study of 30 patients with miscellaneous diseases and prothrombin deficiency, the following impressions were obtained:

1. 2-methyl-1,4-naphthoquinone, its dipropionyl derivative, and its sodium bisulfite derivative have satisfactory vitamin K-potency taken orally or parenterally in dosage of 1 to 4 mg. daily.

2. No evidence of toxicity was seen in giving as much as 20 mg. of 2-methyl-1,4-naphthoquinone intravenously in one dose.

3. The prothrombin response to treatment appears within twenty-four hours and lasts less than a week after vitamin K therapy is ended. The daily administration of vitamin K is desirable in treating hypoprothrombinemia.

4. Prothrombin deficiency refractory to treatment may be seen in severe liver damage and in chronic sepsis.

5. The effectiveness of 2-methyl-1,4-naphthoquinone taken by mouth is increased by taking deoxycholic acid or bile salts, even in the absence of jaundice.

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The following is a description of the results we secured in this experimental study:

Fig. 1A shows the gross and microscopic sections of the kidney of a rabbit sacrificed two days after nephrotomy had been performed with the scalpel. The line of incision extends from the cortex into the renal

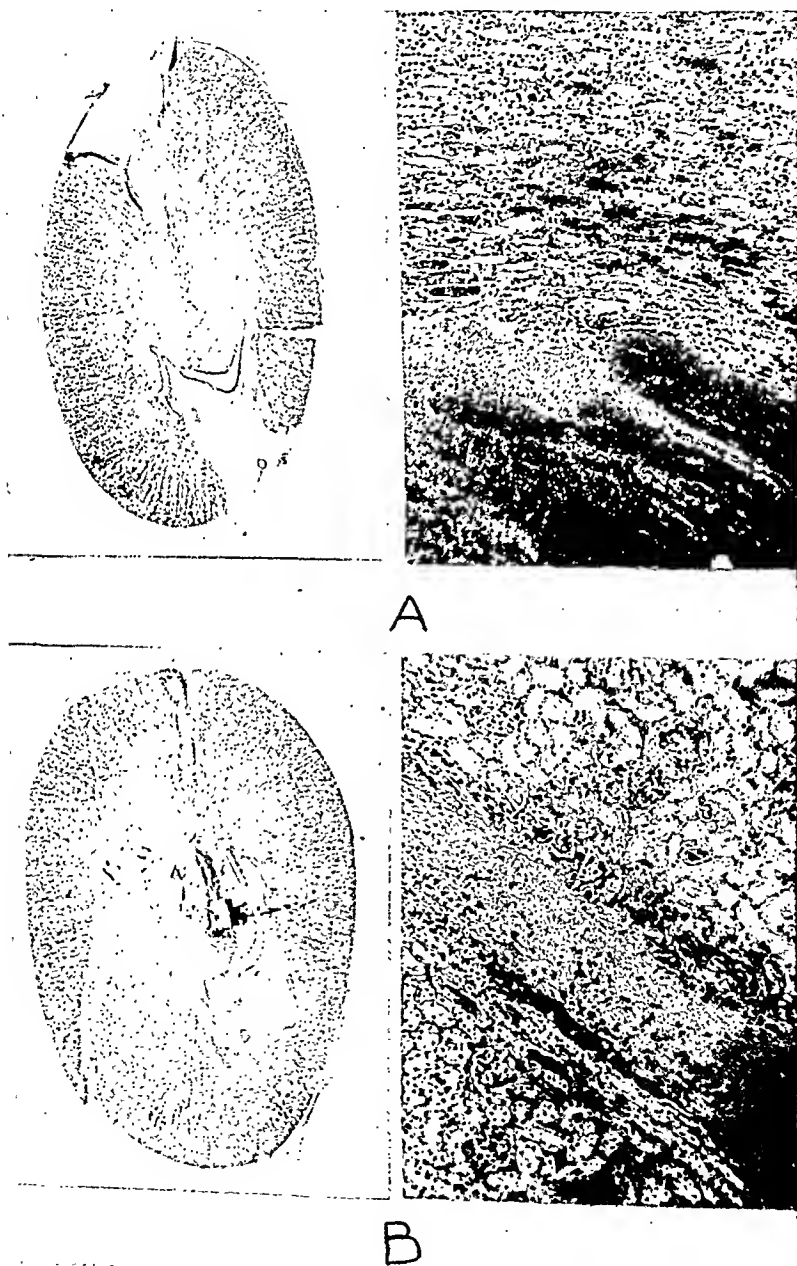


Fig. 1.

# RELATIVE MERITS OF THE SCALPEL AND HIGH FREQUENCY CURRENT IN NEPHROTOMY

## EXPERIMENTAL STUDY

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THE increasing trend toward conservative renal surgery, with particular reference to renal lithiasis, and the relatively high mortality rate following extensive nephrotomies prompted this study. That conservative kidney surgery for patients with renal calculus disease is justifiable cannot be doubted. However, as pointed out by Scholl<sup>1</sup> and others, extensive nephrotomy is a hazardous operation due largely to four factors: (1) primary hemorrhage, (2) cortical sepsis, (3) loss of functioning renal tissue by incision or sutures, and (4) secondary hemorrhage.

It was our purpose in this experimental work to study histologically the relative amount of primary hemorrhage, intrarenal extravasation of blood along the lines of incision, infarction of renal tissue, and the relative rate of healing.

Experimental nephrotomies were performed on rabbits with the high frequency cutting current and with the scalpel, two rabbits being used for each procedure. These rabbits were sacrificed at time intervals of two, four, seven, fourteen, thirty, and sixty days. The essential findings of the sections which were taken from the kidney operated upon at various levels will be described below.

De Vincentiis<sup>2</sup> performed a similar experiment and concluded that there was considerably more necrosis extending diffusely into the renal parenchyma from the line of incision in operations in which the high frequency cutting current was used than in operations in which the scalpel was employed. He also noted that healing was retarded somewhat in those cases in which the high frequency cutting current was utilized. Recognizing the advantages of the high frequency cutting current with reference to its hemostatic action, de Vincentiis felt that it should not be employed in kidney surgery for the above reasons. However, as pointed out by Ellis,<sup>3</sup> it should be remembered that a relatively clean cut can be produced with a spark-gap machine by increasing the frequency of oscillation and lessening the amperage.

Before beginning this study, we experimented with the high frequency machine on the kidneys of rabbits until we found the ideal current to be used; that is, one in which the cut was clean with very little evidence of gross coagulation.

The microscopic section shows the line of incision to be very narrow with evidence of scar tissue formation. The sharp line of demarcation from the incision and the adjacent kidney tissue is again pronounced. Infarcted renal tubules are also seen in this section.



A



B

Fig. 2.

papilla and is represented by an extensive area of hemorrhage without evidence of organization. There is extensive extravasation of red blood cells within the kidney tissue adjacent to the line of incision. A large v-shaped area of infarction is present, extending from the cortex into the medullary substance. It is of interest to note that such areas of infarction were more frequently observed in operations in which the scalpel was used in contrast to operations in which the incision was made with the high frequency current.

We believe that there are three definite factors producing such areas of infarction: (1) The site at which the incision is made in the kidney may cut off circulation to a given area; (2) the placing of mattress sutures also impairs renal circulation to definite areas; and (3) with more pronounced degrees of intrarenal hemorrhage seen where the scalpel has been used, there is increasing intrarenal pressure which, we believe, results in impairment of circulation to certain regions. This factor has been consistent in our studies.

Fig. 1B represents the gross and microscopic sections from the kidney of a rabbit sacrificed two days after operation which was performed with the high frequency cutting current. The line of incision is represented by a narrow zone of hemorrhage with a small area of infarction in the region of the cortex. Microscopically, the line of incision is sharply demarcated from the adjacent kidney tissue. This condition is to be expected when one considers the coagulating effect of high frequency current where the spark-gap machine is used.

Fig. 2A represents the gross and microscopic sections of the kidney of a rabbit sacrificed four days after operation in which the scalpel was used. Fig. 2B represents sections from the kidney of a rabbit sacrificed at the same time interval, but in which the operation was performed with the high frequency cutting current. In the sections taken from rabbits operated upon with the scalpel, it is interesting to observe the broader zone of hemorrhage representing the line of incision, associated with a larger area of infarction. An area of necrosis is seen in the tip of the papilla in Fig. 2A.

Fig. 3A represents the gross and microscopic sections taken from the kidney of a rabbit sacrificed seven days after operation which was performed with the scalpel. A large area of infarction and necrosis is evident in the cortical region. The remainder of the line of incision is barely perceptible except in the papilla where an area of necrosis is discernible. The microscopic section shows quite a broad area representing the line of incision, with no evidence of healing. There is, however, superimposed infection as evidenced by considerable leucocytic infiltration, fibrin, and edema.

Fig. 3B represents the gross and microscopic sections taken from the kidney of a rabbit sacrificed seven days after operation which was performed with the high frequency cutting current. The gross section presents an apparently normal kidney with no evidence of red blood cells.

ably the etiologic factor producing this infarction. To the right of the infarcted area is a region of atrophy of the kidney tissue which is due to partial impairment of circulation to this region. The microscopic section demonstrates this atrophy of kidney tissue.

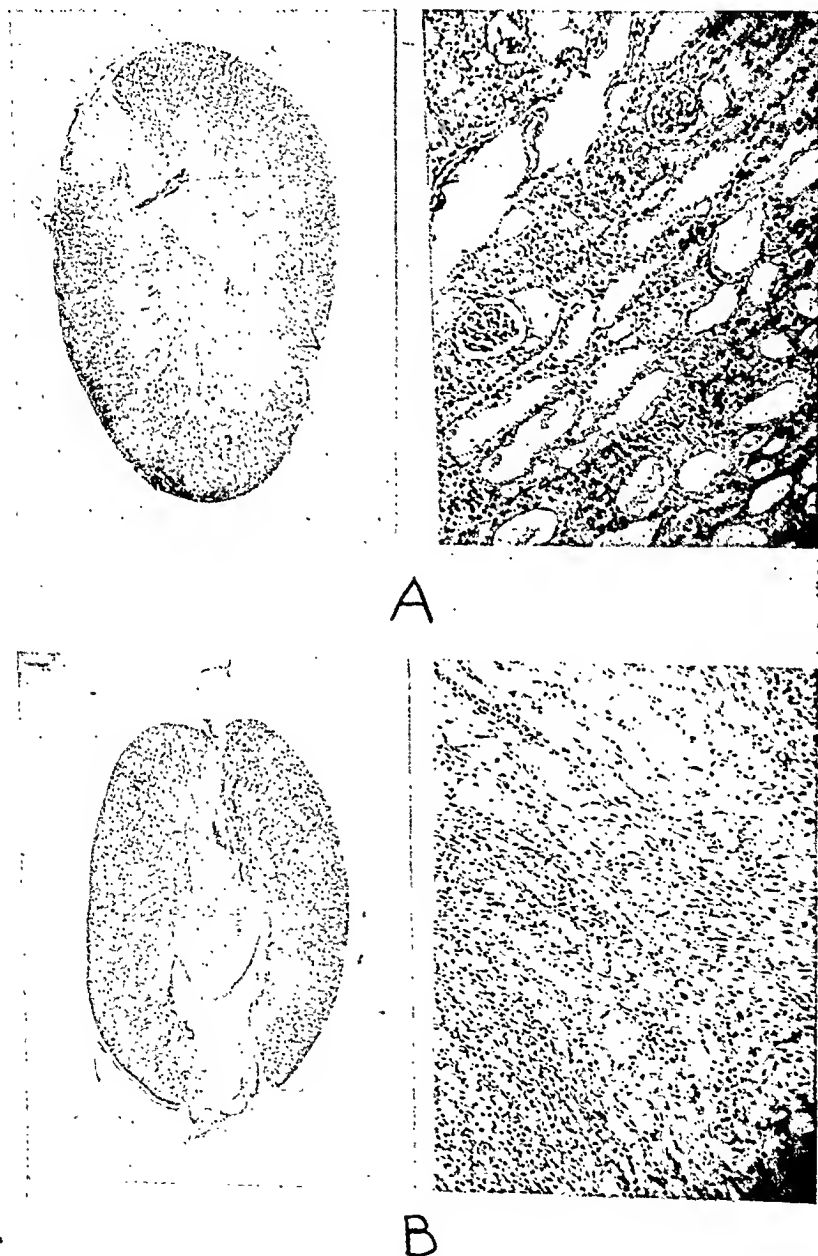


Fig. 4.

Fig. 4.1 represents the gross and microscopic sections taken from the kidney of a rabbit sacrificed fourteen days after operation which was performed with the scalpel. The gross section shows a large area of infarction extending from the cortex into the medullary substance. A suture is seen traversing the area of infarction at its apex and is prob-

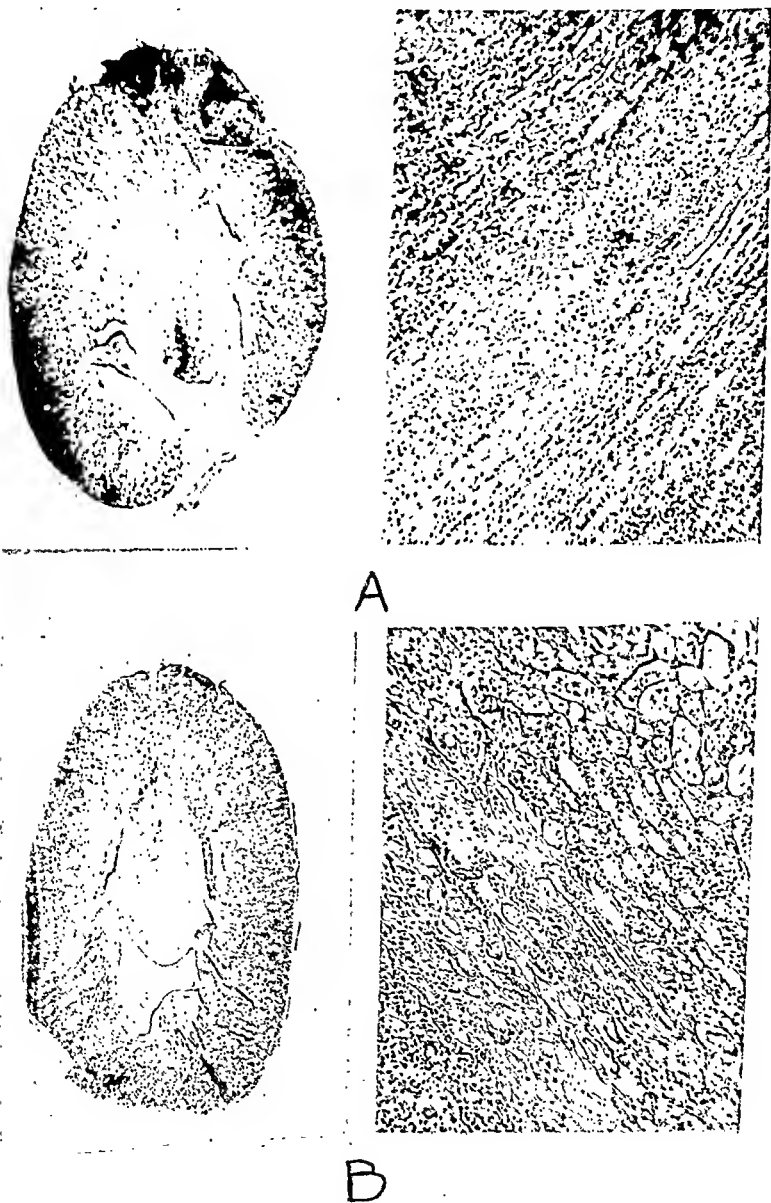


Fig. 3.

Fig. 4B shows the gross and microscopic sections from the kidney of a rabbit sacrificed fourteen days after operation performed with the high frequency cutting current. The line of incision is represented by scar tissue formation and a narrow zone of infarction.

Fig. 5A represents the gross and microscopic sections taken from the kidney of a rabbit sacrificed thirty days after operation which was performed with the scalpel.

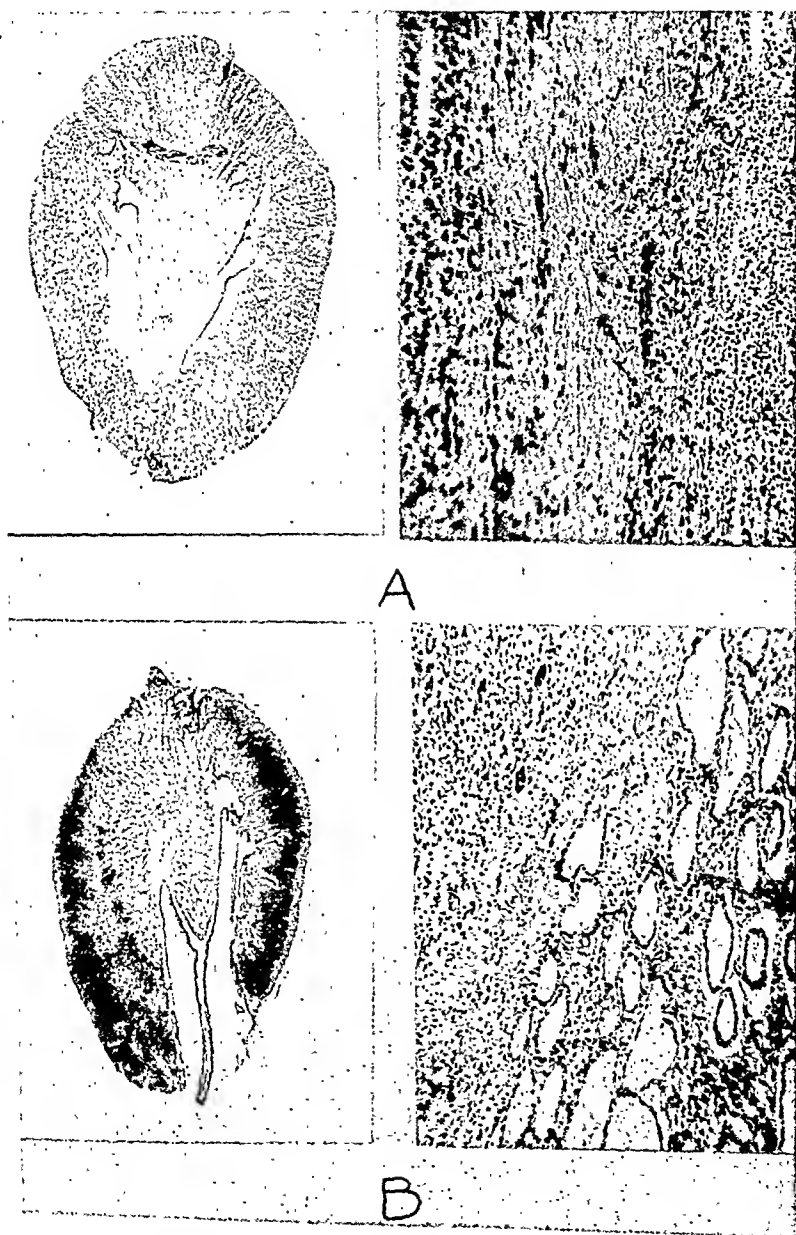
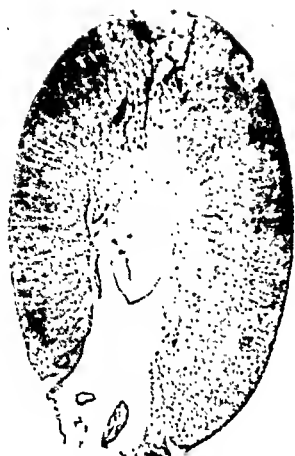
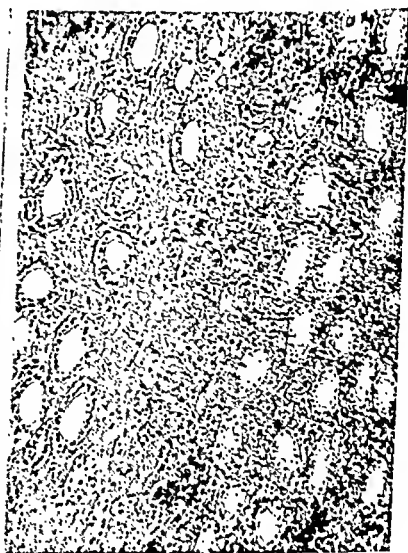
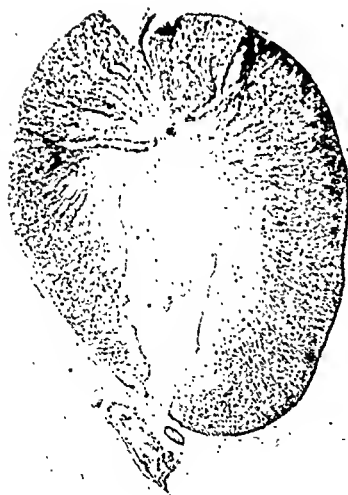


Fig. 6.



A



B

Fig. 5.

# Editorial

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## Anesthesia in Medical Preparedness Program

IN THE present preparedness parade the surgeon must march in the front rank. However much we may deplore it, preparations for war mean preparations to furnish the surgeon with unlimited numbers of injured people for whom he must care. In the rush of plans to transpose surgery from a peacetime to a wartime basis, a certain element of hysteria is likely to creep in. We are apt to lose sight of details of prime importance. The matter of anesthesia is one such detail. In civil practice every surgeon has provided himself with what he believes to be a satisfactory solution of the anesthesia problem. Transferred to military duty, he can scarcely hope to take with him an intact surgical team as he has organized it at home. Even if this were possible, anesthesia for mutilated fighters and their victims is a more complicated problem than civilian practice of the relief of pain. The care of respiratory embarrassment in a patient in a civilian hospital is difficult. When the face is shot away or the pleural cavity laid open, maintenance of the respiratory function taxes the skill of the most adept.

We ought to profit by previous experience. In our own army in France in the summer of 1918, after a breakdown in anesthesia service, it was decided that more medical men must be especially trained in anesthesia. Field schools of anesthesia for medical officers were established at camps in this country, but without facilities for practical instruction in operating rooms. Peace came too soon to observe the benefits of such instruction. The arrangement of space used for surgery in France in 1918 was found to be important. Large operating rooms in which several surgical teams could work simultaneously proved of advantage for several reasons, one of which was that one capable anesthetist thus simultaneously can supervise several anesthetized patients when necessary. A similar plan has been found useful in England during the past year. The following quotation from a personal letter from London is pertinent:

"One huge ward at Epsom has been converted to take 6 operating tables . . . At St. Thomas' Hospital we have a very nice emergency theatre, providing for 5 tables in a row with sliding curtains between . . . The usual military practice here is for a full colonel to be in charge of a hospital in a purely administrative capacity. Then there is a lieutenant colonel in charge of medicine and another in charge of surgery who actively run and direct everything apart from administration. Below them the personnel is much the same on the two

Fig. 5*B* represents sections taken at the same time interval, the operation being performed with the high frequency cutting current. The line of incision in both cases is well healed and is represented by scar tissue.

Fig. 6*A* represents sections taken from the kidney of a rabbit sacrificed sixty days after operation which was performed with the scalpel, while Fig. 6*B* shows sections taken from the kidney of a rabbit sacrificed at a similar time interval, the operation being performed with the high frequency cutting current. Again one notes good healing in both cases.

No animals died postoperatively following operations performed with the high frequency cutting current. However, the immediate operative mortality following operations which were performed with the scalpel numbered four animals, all of which died of hemorrhage and shock.

#### CONCLUSIONS

1. There is less primary hemorrhage when an extensive nephrotomy is performed with the cutting current than when the scalpel is used.
2. Extravasation of blood into the renal tissue adjacent to the line of incision is greater when the scalpel is used.
3. There is less infarction adjacent to the line of incision when the high frequency current is employed.
4. Healing is more or less comparable in each case.

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# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## RECENT ADVANCES IN THE STUDY AND MANAGEMENT OF TRAUMATIC SHOCK

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### I. INTRODUCTION

SHOCK is a subject that is of importance not only during war but in peacetime. It is the major cause of death in all types of injuries and is at present a limiting factor in the operability of many conditions. Surgery has advanced rapidly during the past century when one by one the shackles of pain (anesthesia), infection (antisepsis and asepsis), and, more recently, thrombosis (heparin) were removed. If the danger of shock were out of the way, it is difficult to predict how much the range of operability of morbid processes might be increased.

To review the entire literature on shock would be a herculean task beyond the scope of the present paper. Advances both in the understanding and treatment of shock have been so rapid during the past decade that this review will consider mainly the advances made in that period, 1930 to 1940. This is especially advisable because certain papers appearing at the beginning of the decade brought fresh light to the old subject, the cause of shock. It will be impossible to deal immediately with these most recent advances without a brief historical résumé as a point of departure.

### HISTORICAL RÉSUMÉ

A better idea of the advances made in an understanding of shock during the past decade can be had after a brief historical résumé of previous work. Not only is this true because of the contrast in ideas in many cases, but because in others the older workers really laid better foundations for present knowledge than casual study would lead one to realize. It might be interesting arbitrarily to divide the history of shock into four periods.

1. *Early Period.*—From the time of James Latta (1795), of Edinburgh, who used the word "shock," and other early writers down to the time of Fischer (1870) may be considered the *descriptive period*.

services. Take the surgical side: Two majors are general surgical specialists. One major is an anesthetic specialist with additional captains and lieutenants according to the size of the hospital. The anesthetist major is responsible for his underlings, and they may run 6-9 tables."

The number of physicians in the United States well trained in anesthesia is now much greater than in 1918. Nevertheless, special courses of instruction ought to be established at once so that young medical officers already partly trained and those wishing to render such service may be especially prepared for wartime duty.

In the long past anesthesia has been looked upon as an operating room service solely. The term "anesthesiology" has been utilized in recent years to designate a larger service. It includes skill in the use of the various technical maneuvers and drug administration found useful in putting patients "at ease" during surgery, but it goes much further than that. The supervision of physiologic processes, especially the function of respiration, during depression following head and chest injuries; after drug administration for pain relief; after gas poisoning; in shock and in pneumonia, involves the use of methods familiar to the anesthetist. The insertion of artificial airways in the presence of blood and mutilation of the respiratory tract, the administration of artificial atmospheres, the cleansing of the tracheobronchial tree when contaminated, artificial respiration, the injection of locally acting anesthetic drugs to relieve the pain of fractured ribs and other bones, all these are technical procedures familiar to the well-trained anesthetist and useful for the safety and comfort of the injured. In military practice such service ought often to be rendered under field conditions. The need for medical officers especially trained along these lines is obvious.

It is highly desirable that those who are formulating plans for medical military preparedness may include the assignment of at least one well-trained physician as anesthetist to each hospital unit. Arrangements ought also to be made for the training of an adequate number of medical officers in anesthesiology so that surgeons may be left free of the worry of providing such service for themselves. It is to be hoped that the present mobilization may include provision for such special training and assignment of medical officers from the beginning, without waiting for the demonstration of such need after field operations have begun.

—*Ralph M. Waters, M.D.*  
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TABLE I  
THEORIES OF SHOCK

- 
1. Nervous
    - Vasomotor exhaustion
      - Mitchell, Morehouse, and Keen (1864)
      - Fischer (1870)
    - Exhaustion
      - Crile (1897-1920)
      - O'Shaughnessy and Slome (1935)
    - Inhibition
      - Meltzer (1908)
  2. Fat embolism
    - Bissell (1917)
    - W. T. Porter (1917)
  3. Arterial vasoconstriction and capillary congestion
    - Mapother (1879)
    - Malcolm (1893-1909)
    - Starling (1918)
    - Erlanger, Gesell, and Gasser (1919)
  4. Acapnia
    - Henderson (1908)
  5. Acidosis
    - Cannon (1919)
  6. Hyperactivity of adrenal medulla
    - Bainbridge and Trevan (1917)
    - Freeman (1933)
  7. Exhaustion of adrenal medulla
    - Sweet (1918)
  8. Adrenal cortical insufficiency
    - Swingle, Pfiffner, et al. (1933)
  9. Traumatic toxemia
    - Cannon, Bayliss, and British Medical Research Committee (1918)
  10. Traumatic metabolites giving capillary atony and tissue anoxia
    - Moon (1932-1938)
  11. Local fluid loss
    - Phemister (1927-1930)
    - Blalock (1930)
  12. Progressive oligemic anoxia
    - Harkins (1940)
- 

This idea is supplemented by the finding in shock patients that the nerve cells of the brain show pathologic changes at necropsy. These changes were assumed to be evidence of exhaustion. This finding, upon which several books were based, in turn was founded for many years on the observations of one neuropathologic technician. Crile's first book appeared in 1899 and Lockhart Mummery (1905) agreed with the ideas of Crile on vasomotor exhaustion, with the result that in England this theory became known as the Crile-Mummery hypothesis as to the origin of shock.

Gray and Parsons (1912) recognized other factors causing nervous change, stating in this regard: "Anaemia and starvation of the central nervous system—if this is carried to a sufficient degree, the recovery of the centers is rendered impossible." These authors also found that, if a severely shocked animal was subjected to a needle puncture into the floor of the fourth ventricle, a marked rise in blood pressure occurred.

2. *1870 to 1898.*—These years involved much speculation and some experiment. Most of the theories propounded during this period implicated nervous impulses as being the cause of shock. Fischer (1870), whose work may be said to have introduced the period, believed in vaso-motor exhaustion and stagnation of blood in the splanchnic areas. The latter theory is fallacious and probably originated in the fact that in intestinal manipulation shock stagnation occurs because of local fluid loss (early workers showed as much as 37 per cent stagnation), but in shock of other types does not occur, as shown by the clinical observations of Wallace, Fraser, and Drummond (1919). During this period Gussenbauer's review and other work included the following:

Early experimental observations on the blood dilution accompanying hemorrhage and concentration associated with shock were made by Sherrington and Copeman (1893). Turek (1897) recognized the importance of chilling in the production of shock and devised an apparatus to irrigate with warm (130° F.) water the stomachs of patients operated upon.

3. *The Experimental Physiology Period, 1899 to 1923.*—The work of this period was introduced by Crile's first book, climaxed by the studies of the Shock Committee during World War I and summarized by Cannon's monograph in 1923. The article of Power (1906) gives an idea of the views early in this period.

Following this there was a period of relative inaction, before the final period.

4. *The Experimental Clinical Period, 1930 to 1940.*—These last two periods are discussed in more detail below. Heinemann (1938) has given an excellent résumé of the history of shock.

*The Exhaustion Theory of Shock, the Crile-Mummery Hypothesis.*—One of the differences between Crile's work and that of others was that, instead of propounding his theory in a series of articles, he advanced it in a series of books. Crile has published almost as many books on shock as all other writers combined. All of these books contain data to support his exhaustion theory, which is also propounded in a series of articles, including those of Crile (1923), Crile (1924), and Crile, Rowland, and Telkes (1928).

The views of Crile may be seen most readily by reading the following quotation from one of his articles (1924): "The body as a whole is an electro-chemical mechanism, the positive pole being the brain, the negative the liver, the connecting wires the nerves, the salts in solution the electrolytic fluid in which the electro-chemical mechanism is immersed. When either pole, i.e., the liver or the brain, is removed or destroyed, the organism perishes."

Crile and Hosmer (1919) reported that in shock the electric conductivity of the brain is decreased and that of the liver increased.

proportion of blood in the arteries and capillaries and that in the venous trunks gave a rough estimate of the depth of the shock." Crile also said that, when the splanchnic area was not involved in the manipulations of an experiment, "autopsies did not reveal a condition of vascular distension in this area different from that of other areas."

It is noteworthy that Henderson was cognizant of the lack of vasomotor collapse in shock as early as 1908, stating that the blood pressure fall in shock "is not due to abolition of the peripheral resistance in the arterial system. No inhibition or fatigue or failure of any sort occurs in the vasomotor system. On the contrary, this mechanism is intensely active in an effort to compensate the lessened blood stream."

Malcolm was also an early advocate of the importance of fluid loss being a factor in shock. He listed it more as a secondary phenomenon than as an initiating cause. As evidence for this he cited Crile's observation that saline solution was often of little value in late cases, apparently passing readily out of the veins, and pointed out that in formulating his theory, Crile "did not even mention the possibility that the fall of blood pressure might be due to a loss of fluid."

Malcolm then concluded: "A fall of carotid pressure arising from an intense vascular contraction is possible only if fluid escapes freely from the vessels into the tissues or out of the body. The chief danger of developing shock is that the tissues may be starved by arterial contraction."

Malcolm then advised against the indiscriminate use of vasoconstrictors. The remarkable thing about this work, which was well in advance of its time, is that, as Malcolm himself admitted, it was based entirely on clinical observations. Since those with whom he was arguing had performed numerous experiments, this shows once more that accurate clinical observation with carefully drawn conclusions is better than improperly controlled or incorrectly interpreted experiment.

In 1908 two prominent theories of shock appeared, the *acapnia theory* of Henderson and the *inhibition theory* of Meltzer. The research of Henderson (1908) is classic in the field of shock. He showed that acapnia will produce shock, and, while it has since been demonstrated that shock may occur without acapnia, yet these studies of Henderson contain several fundamental observations on circulatory changes in shock that represent important discoveries. The review of this theory written by Henderson in 1913 is of especial interest. Meltzer's theory can best be explained by the following direct quotations.

"In shock the activity of the functions is depressed or suspended. . . . The various injuries which are capable of bringing on shock, do so by favoring the development of the inhibitory side of all the functions of the body. . . . With regard to shock, our theory assumes that the injuries which produce shock disturb the equilibrium, causing a tendency toward

This led them to conclude that the vasomotor center is still active in the most severe degree of collapse and even in terminal states. The marked Traube-Hering waves observable in profound shock in many of their tracings corroborated this conclusion. On the basis of careful cytologic examination of animals and human beings, Gray and Parsons (1912) concluded: "Fatigue of the nerve cells does not occur in shock."

Janeway and Ewing (1914) also opposed Crile's theory, stating: "Within the time limit which we have adopted in these experiments, which is quite sufficient from the practical point of view of the operating surgeon, the exhaustion of the nerve centres by afferent stimulation of sensory nerves is a wholly negligible factor in the production of shock."

Irrespective of the merits of Crile's theory, his efforts at blocking painful stimuli went far in reducing the trauma attendant on operation. This, no matter what theory one upholds, has been shown by modern experiment to be of importance in preventing shock. Even if wrong, from the practical standpoint, the Crile-Mummery hypothesis has proved to be a useful error.

During the next few years after Crile's first publication, numerous studies were made that showed that the vasomotor center, at least, is not exhausted in shock; in fact, that it is almost overactive. The research of Porter (1907-1908) is of interest in this regard. As later quoted by Janeway and Ewing (1914): "Porter obtained in numerous experiments a greater percentage rise of blood pressure by stimulating the sciatic or vagus or splanchnic, or a greater percentage fall by stimulating a depressor nerve after the blood pressure had been reduced in shock than before the shock had been produced. . . . Nevertheless, the absolute rise or fall in Porter's experiments was very great and the experiments furnish strong evidence of the absence of fatigue in the primary stages of shock."

Just as Porter (1907-1908) claimed to show explicitly that in shock the vasomotor center is not exhausted and, therefore, implicitly that the peripheral vessels are not paralyzed, so Seelig and Lyon (1909) claimed to show explicitly that the peripheral vessels are contracted and implicitly that not all the vasomotor centers can be exhausted. The classic observations of Malcolm (1893, 1905) on the constriction of peripheral vessels in shock are of great interest. Sheen (1906) tended to agree with Malcolm in a purely theoretical paper.

The article of Malcolm (1910) stands out as one years ahead of its time and deserves quotation. Malcolm discussed Crile's paper on the theory that the vasomotor centers are paralyzed in shock. He pointed out two statements in Crile's works in opposition to this conclusion. Crile asserted that both before and after death from shock "the arteries were quite empty, the tissues pale. There was a manifest transference of the blood from the arteries and the capillaries to the veins. . . . The relative

proportion of blood in the arteries and capillaries and that in the venous trunks gave a rough estimate of the depth of the shock." Crile also said that, when the splanchnic area was not involved in the manipulations of an experiment, "autopsies did not reveal a condition of vascular distension in this area different from that of other areas."

It is noteworthy that Henderson was cognizant of the lack of vasomotor collapse in shock as early as 1908, stating that the blood pressure fall in shock "is not due to abolition of the peripheral resistance in the arterial system. No inhibition or fatigue or failure of any sort occurs in the vasomotor system. On the contrary, this mechanism is intensely active in an effort to compensate the lessened blood stream."

Maleolm was also an early advocate of the importance of fluid loss being a factor in shock. He listed it more as a secondary phenomenon than as an initiating cause. As evidence for this he cited Crile's observation that saline solution was often of little value in late cases, apparently passing readily out of the veins, and pointed out that in formulating his theory, Crile "did not even mention the possibility that the fall of blood pressure might be due to a loss of fluid."

Maleolm then concluded: "A fall of carotid pressure arising from an intense vascular contraction is possible only if fluid escapes freely from the vessels into the tissues or out of the body. The chief danger of developing shock is that the tissues may be starved by arterial contraction."

Maleolm then advised against the indiscriminate use of vasoconstrictors. The remarkable thing about this work, which was well in advance of its time, is that, as Maleolm himself admitted, it was based entirely on clinical observations. Since those with whom he was arguing had performed numerous experiments, this shows once more that accurate clinical observation with carefully drawn conclusions is better than improperly controlled or incorrectly interpreted experiment.

In 1908 two prominent theories of shock appeared, the *acapnia theory* of Henderson and the *inhibition theory* of Meltzer. The research of Henderson (1908) is classic in the field of shock. He showed that acapnia will produce shock, and, while it has since been demonstrated that shock may occur without acapnia, yet these studies of Henderson contain several fundamental observations on circulatory changes in shock that represent important discoveries. The review of this theory written by Henderson in 1913 is of especial interest. Meltzer's theory can best be explained by the following direct quotations.

"In shock the activity of the functions is depressed or suspended. . . . The various injuries which are capable of bringing on shock, do so by favoring the development of the inhibitory side of all the functions of the body. . . . With regard to shock, our theory assumes that the injuries which produce shock disturb the equilibrium, causing a tendency toward

inhibition. It certainly does not mean reducing the function to a single principle, to inhibition alone; it only means shifting the tendency toward inhibition. . . . The assumption that the insufficient activity of several functions during shock is due to a preponderating inhibitory influence refers only to the primary effect. . . . During the course of shock other influences must become secondarily active . . . anemia, asphyxia or even fatigue . . . might become operative."

*The War Years, 1914 to 1918.*—These years saw a continued increase in interest in shock. It is worthy of note that most of this was on the side of the allied armies. The work of Mann (1915) was the earliest on the decrease in bleeding volume (and hence, inferentially, of the blood volume). Mann showed that in a normal dog 66 per cent of the blood could be obtained from the femoral artery, while in an animal in which the viscera had been exposed until the clinical signs of shock were present, but in which the "vasomotor reflexes are as active or even more so than in the normal condition," only 28 per cent of the blood could be recovered. Shock produced by overdosage of ether or cervical cord section produced no such drop. Furthermore, Mann attributed the low blood volume and shock to a local loss of circulatory fluid.

The comment of Gatch in the discussion of this paper reveals how advanced the views of Mann were. Discussing the shock due to exposure of viscera, Gatch said: "The gist of Mann's article is that shock and hemorrhage are practically identical, that experimental shock is simply due to an extensive extravasation of the elements of blood into the peritoneal tissues, that this change is due to a traumatic inflammation and that the central nervous system has little to do with the condition."

Bloodgood in the same discussion disagreed with these conclusions, but Mann stuck to his views as shown by a later paper (1918).

Several other bits of information were obtained at this time. Guthrie (1917) demonstrated quantitatively that vasomotor tone is present in shock. Guthrie (1918) found no hemoconcentration accompanying experimental shock due to excessive nerve stimulation. The experiments of Guthrie (1918) on absence of shock following intravenous lactic acid injection tended to discount the acidosis theory. Porter (1916) emphasized the importance of observation of the diastolic pressure in determining the seriousness of shock.

Henderson, Prince, and Haggard (1917) made early observations on the metabolism of burns. They found that "the condition of shock involves a profound depression of metabolism, the oxygen consumption falling 45 per cent in one experiment and 50 per cent in another. This depression of metabolism is progressive, and ends in death."

The series of seven articles appearing in the *American Journal of Physiology* (1919) from the laboratory of Joseph Erlanger, of St. Louis, with the cooperation of Gesell, Gasser, and Meek marks an important era

in the understanding of the physiologic changes in shock. Erlanger and his associates studied shock after manipulation of the intestines, adrenalin injection, and aortic and caval occlusion. They noted that, following manipulation of the intestines, "a considerable loss of fluid from the exposed bowel occurs as a result of transudation through the serous surface, and presumably into the tissues also." Gasser, Erlanger, and Meek (1919) found that 20 per cent acacia was of benefit in experimental shock. Erlanger and Gasser (1919) showed by quantitative experiments that sodium bicarbonate injections increased the mortality following shock production. The studies of Gesell (1918, 1919) on the decrease of the volume flow of blood in shock and hemorrhage are classic. In 1918 Gesell found a marked reduction of volume flow in peripheral organs while the blood pressure was still well maintained.

At about this same time Porter (1917-1919) presented his *fat embolism theory* of the origin of shock. It is of interest that Mansell-Moullin (1894) mentioned fat embolism as a possible cause of shock.

Also at this time several important advances in treatment were introduced. The use of gum acacia was begun and blood transfusion was developed. General care was improved. The idea of Brown (1917) that, since shock is due to exhaustion, operative shock can be prevented by jejunal feeding of peptonized milk during the operation is quite out of date, despite the fact that the method may have other virtues (e.g., treatment of chronic hypoproteinemia).

The reports of the Medical Research Committee in 1919 mark an historic epoch in the study of shock. While many of these studies, performed under the exigencies and haste caused by the demands of war, were later proved inaccurate, probably more real advances and correct observations were reported in these few green-covered pamphlets than ever before or since. The work of Wallace, Dale, Laidlaw, Richards, Bayliss, Cannon, Keith, McNee, Sladden, McCartney, Telfer, Cowell, Fraser, Hooper, Drummond, Taylor, Robertson, Bazett, Bock, and Mott represents the united efforts of men from many disciplines of science to solve a gigantic problem.

A marked decrease in body temperature is often a striking feature of secondary shock. Henderson, Prince, and Haggard (1917) in a preliminary note mentioned a marked drop in metabolism in two dogs in shock. In experiments on cats under urethane anesthesia, Aub (1920) found a marked fall in the rate of basal metabolism after trauma to an extremity. The degree of fall was roughly proportional to the severity of shock produced, and recovery from shock after blood transfusion was usually associated with a prompt return of the metabolic rate to a normal level.

Aub (1920) also noted that the blood pressure change is often a late sign of shock, stating: "After muscle injury the metabolism may be

reduced before a great fall in blood pressure has occurred. . . . The volume flow of blood [italics Aub's] determines the oxygen delivery to the tissues, and this may vary to some degree without corresponding variation in blood pressure."

Aub (1920) reported that in animals with marked muscle trauma but without true shock only slight changes in the nonprotein nitrogen, urea, creatine, and sugar values in the blood occurred. These constituents, especially the creatine and the sugar, rose markedly as shock developed. He concluded that "the marked rise in creatine is direct evidence of the presence in the blood of products of muscle necrosis, and is therefore suggestive evidence for the theory of the chemical cause of traumatic shock."

As long ago as 1918, several French observers ascribed shock phenomenon to a liver insufficiency and Aub (1920) cited this as a possible cause for the hyperglycemia often observed. Richet and Flament (1918) noted toxic changes in the liver following shock.

*Work on Shock in the Early 1920's.*—Several isolated articles of interest appeared at about this time. Bock (1921) showed that, while the erythron may vary widely in medical cases, the volume of the blood plasma remains remarkably constant. The studies of Cannon and Cattell (1922) on blood pressure and the use of morphine in shock are of importance. That small hemorrhages will actually increase the plasma volume, probably because of inflow of tissue fluids, was shown by Carrier, Lee, and Whipple in 1922. A year later appeared Cannon's monograph, *Traumatic Shock*. This book summarized all the work done on shock during the War and all the output of the study stations at Dijon and Bethune. It was so complete that it seemed to close a chapter in the study of shock. In the remaining years of the 1920's relatively little was published on the subject and it remained for the 1930's to usher in the renewed interest that is to be reviewed in the present paper.

#### CLASSIFICATION

Classifications of shock fall into three main groups. The first is determined by origin; i.e., traumatic shock, operative shock, burn shock, obstetric shock, medical shock, etc. This is a purely descriptive differentiation. A somewhat more analytical one differentiates primary and secondary shock. Since it has been shown by Harkins (1935) and others that the changes leading to secondary shock begin as soon as the accident or other precipitating factor occurs, this classification is somewhat faulty. The so-called primary shock, then, is of two types: first, the pseudoshock state in a patient whose condition is one of uncomplicated blood pressure fall and in whom any relation to true shock is only coincidental; and second, the period in a truly shocked patient where the secondary shock state is in progress of development but is not yet obviously manifest.

TABLE II  
THEORIES OF SHOCK  
ROOME'S "UNIFIED THEORY OF SHOCK"

STAGE 1	STAGE 2	STAGE 3	STAGE 4
<i>Several causes: (local loss of fluid, including hemorrhage in traumatic shock; others in other types) dehydration or starvation contributory</i>	<i>Reduced circulating blood volume: vasoconstriction by sympathico-adrenal action contributory?</i>	<i>Decreased blood flow, capillary damage and increased permeability: Pre-existing reduced flow, infection or disease, and anoxemia contributory</i>	<i>Peripheral circulatory failure and death</i>

This second classification is faulty in the first instance in that the condition is primary, it is true, but not shock; while in the second instance it is shock but is not primary. It has served a useful purpose, however, in allowing work such as that of Blalock (1933), Roome, Keith, and Phemister (1933), and Phemister and Livingstone to differentiate between the changes occurring in the two types. It would be well to abandon the term primary shock. The word shock might well not be applied at all to the pseudoshock condition now called primary shock. "Developing" or "impending" shock would be better names for the early stages of actual shock.

The third, and possibly the best, classification of shock is that of Blalock (1934), which is as follows:

1. *Hematogenic Type (Oligemic Type).*—This comprises what is usually called secondary, traumatic, and operative or surgical shock. The essential feature is the oligemia as the initiating factor with the blood pressure fall secondary.

2. *Neurogenic Type.*—This comprises what is usually called primary shock, and its essential feature is the primary fall in blood pressure. If allowed to remain at a low level for a prolonged period, this will lead to oligemia secondarily. Shock due to spinal anesthesia or fainting is of this type.

3. *Vasogenic Type.*—Histamine shock is of this type, the action being directly on the blood vessels.

4. *Cardiogenic Type.*—In this central type of shock in contradistinction to the three previously cited types of peripheral circulatory failure, the veins are distended. This type is undoubtedly rare.

#### DEFINITIONS OF SHOCK

- Travers (1826) Shock is a species of functional concussion by which the influence of the brain over the organ of circulation is deranged or suspended.
- Delcasse (1834) An arrest of innervation without which all organs pass into insensibility. [An old way of expressing Meltzer's inhibition theory.]
- Gross (1872) A manifestation of a rude unlinging of the machinery of life.

- Picchaud (1880) *Le choc est un état général plus ou moins grave consécutif aux traumatismes, spécialement aux plaies par armes à feu et aux grands écrasements, caractérisé par l'affaiblissement des pulsations du cœur, l'abaissement de la tension, la pâleur des tissus, un certain degré d'ancsthésie joint à la faiblesse musculaire, avec conservation de l'intelligence.*
- Mansell-Moullin (1882) A sudden check to the circulation brought about through the agency of the nervous system.
- Roger (1892) *Le choc est un état morbide qui peut se produire à la suite de fortes excitations du système nerveux et qui est caractérisé par un ensemble d'actes inhibitoires dont un seul, l'arrêt des échanges entre le sang et les tissus semble constant et indispensable.*
- Lockhart Mummery (1905) Surgical shock is a condition produced by exhaustion of the vasomotor centers and the resulting great fall in blood pressure.
- Lockhart Mummery (1910) A condition of lowered blood pressure resulting from exhaustion of the vasomotor centers.
- Gray and Parsons (1912) The reaction of the central nervous system to exaggerated or abnormal afferent impulses.
- Morison and Hooker (1915) A low arterial blood pressure of such duration that recovery is impossible.
- Brown (1917) Exhaustion of the food material—the Nissl granules—stored in the nerve cells, more particularly those of the vasomotor centers.
- Quénu (1918) Toxémie traumatique depressive.
- Cannon (1919, 1923) Exemia.
- Meek (1926) A decrease in the effective circulatory volume.
- Schubert (1936) A peripheral circulatory insufficiency.
- Davis (1937) An anoxemia which is the resultant of such factors as oligemia, lowered blood pressure, diminished flow of blood, and peripheral vasoconstriction.
- Tomb (1937) The collapse of the circulation from over-stimulation of the sympathetic nervous system.
- Griswold (1938) A deficiency in circulating blood volume.
- Moon (1938) A circulatory deficiency, neither cardiac nor vasomotor in origin, characterized by decreased blood volume, decreased cardiac output (reduced volume flow) and by increased concentration of the blood.
- Devine (1939) A state of depression of all the reflex arcs accompanied by circulatory depression.
- Minot and Blalock (1940) Peripheral circulatory failure resulting from a discrepancy in the size of the vascular bed and the volume of intravascular fluid.
- Selye, Dosne, Bassett, and Whittaker (1940) A condition of suddenly developing general damage.
- Freeman (1940) The clinical condition characterized by progressive loss of circulating blood volume, brought about by the tissue anoxia which results from inadequate circulation.
- Author (1940) A progressive vasoconstrictive oligemic anoxia.
- ✓ Brief definition An oligemia initiated by traumatic local fluid loss, either whole blood, plasma or both; accompanied by decreased cardiac output, diminished volume flow, lowered venous pressure, decreased oxygen consumption, arteriolar vasoconstriction, acapnia, and secondary blood pressure fall; and perpetuated by a summation of these factors and possibly hyperpotassemia, increased generalized capillary permeability, anoxia, action of tissue metabolites and deficiency of adrenal cortical hormone.
- Descriptive definition

The list of definitions given above is not complete but represents a fair survey of the historical development. Mortimer (1912) criticized Gray and Parsons' definition of shock, stating that it would necessitate considering that operative shock began when the incision was made. This would seem to be unjust and the same criticism could be leveled against some of the more modern definitions. It seems logical to assume that the factors leading to shock actually begin at the time of the original injury, even if they only become manifest later.

The definitions of Cannon, Meek, Schuberth, Freeman and Griswold seem accurate. Tomb's definition is correct but may overemphasize one aspect of the question. Davis' and Moon's definitions are quite complete, and, if Moon would insert the word "progressive" before "hemocentration," I would agree entirely with the modified definition. My definition would apply directly only to Blalock's oligemic type and not so well to his other three types.

Shock must in nowise be confused with the so-called "shock disease" occurring in snowshoe rabbits. This disease is essentially a fatal hypoglycemia of snowshoe hares, caused by the shock of unnatural conditions, and is associated with a disturbance of carbohydrate metabolism resulting from liver degeneration.

#### FOREIGN LITERATURE

Short, of Bristol, England, noted as long ago as 1913 that, judging from the literature, most interest in shock was in the United States and England, and most of that in the United States. This was later true during World War I and thereafter. Parsons and Phemister (1930) noted the interesting fact that shock received relatively little attention from the Central Powers during World War I. The observation of blood pressure during operations introduced into this country by Cushing has only lately been adopted in Europe, and then to a very minor extent. In a few clinics a machine known as the *Kardiotron* keeps a record of blood pressure (Jaeger, 1937). It is quite possible that an explanation for this relative lack of interest in Continental Europe rests in the fact that the clinical men have not paid so much attention to the subject there. Irrespective of the fact that many of Crile's early ideas on shock have not stood the test of time, he served as an inspiring example to interest other surgeons in this country in the subject. Possibly that alone explains a portion of the preponderance of attention received by shock on this side of the Atlantic.

*Germany.*—Most of the best studies on shock are quite recent. Excellent reviews by Liebmann, of Zurich (1937), and of Eppinger (1938) on capillary permeability should be consulted. The fundamental studies of Rein (1937), of Göttingen, are especial contributions of German physiology to the shock problem. Among the German publications, those

of Ewig and Klotz (1932) are of especial importance. These authors studied the postoperative changes in blood and plasma volume by means of the CO method and hematocrit readings and found a reduction in both volumes. Studies have been made in Germany by Ewig (1938) on shock in burns, by Meessen (1938) on insulin shock, by Brüner (1938) on hemorrhagic shock, by Budelmann (1938) on "orthostatic" shock, by Schwiegk (1938) on shock accompanying pulmonary emboli, and by Hansen (1938) and Parade (1938) on obstetric shock. Other studies are considered under the appropriate heading in the present article. During the year 1938-1939, I was in Europe on a Guggenheim Fellowship to study shock experimentally and clinically. In visiting various clinics, the question of shock was usually brought up. The head of one of the largest Viennese surgical clinics was asked if he used blood or saline solution in the treatment of shock. He replied: "Never. My only treatment of shock is to elevate the foot of the bed and put novocain in the wound." This reflects the shock treatment in many European clinics, while others are quite modern.

*France.*—Since World War I, the subject of shock has not been studied as much in France as in this country. The work of Lambret, Driessens, Malatray, and Bizard, of Lille (1936, 1937), forms an exception to this rule. These workers have made an extensive study of the postoperative changes in blood chemistry and their relation to shock. Their observations on the decrease in blood volume attending clinical and experimental shock are quite complete. They recognized the importance of plasma loss and resultant exemia, but also considered a toxic factor due to polypeptidemia.

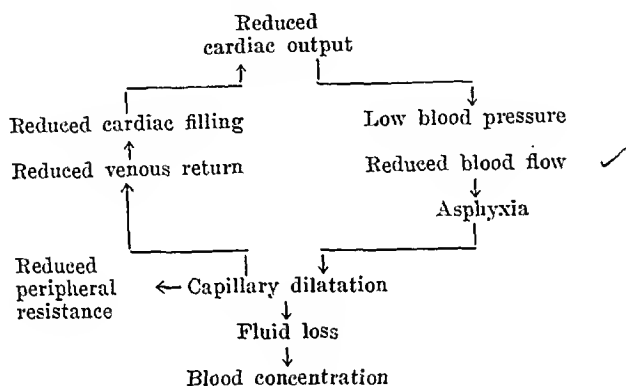
*Great Britain.*—The studies of Holt and Maedonald (1934), O'Shaughnessy and Slome (1935), Marriott and Kekwick (1935, 1936), Bell, Clark, and Cuthbertson (1938), Wilson and Jamieson (1938), and others are so extensive as to necessitate their being considered elsewhere in this paper. Contributions from Sweden, Russia, Italy, Spain, and other countries are also considered elsewhere.

#### REVIEWS

Reviews of the subject of shock include the following: 1930: Blalock; 1931: Blalock, Beard and Johnson; 1932: Rukstinat; 1933: Beard and Blalock, Blalock; 1934: Blalock, Cannon; 1935: Andrews, Dale, Frazier, Holt, Mann and Essex, O'Shaughnessy, Orr, Slome; 1936: Meek; 1937: Boyers, Clement, Tomb; 1938: Gollwitzer-Meier, Heinemann, Kirshner, Koeh, Mahaffey, Roome; 1939: Allen, Cattell, et al., Cressman and Blalock, Devine, Ravdin, Rehn, Meyler; 1940: Wilson, Best and Solandt, Blalock, Harkins, Meakins, Moon, Selye, and Strumia, Wagner and Monaghan. A practical review of shock therapy was given by Fantus and Seed (1940).

The recent review of Peters (1940) very succinctly summarizes the relations of the chemical structure of the blood to surgical problems. A recent review of obstetric shock by Mathews (1939) is of interest. Important editorials on shock appeared in 1917, 1934, 1935, 1939, and 1940. Recent books entirely on shock are those of Moon (1938) and of Seudder (1940). Another book giving major emphasis to the subject is that of Blalock (1940) on *Principles of Surgical Care, Shock, and Other Problems*.

McDowall (1940) in his excellent review on shock depicted the vicious circle ("the death cycle") as follows:



*Moon's Book.*—This book represents such a forceful and in many ways important contribution to shock literature that it deserves a section by itself. Published in 1938, the first book on the subject in any language for fifteen years, it epitomizes the observations made by Moon and his associates at the Department of Pathology of Jefferson Medical College, Philadelphia. The title of the book, *Shock and Related Capillary Phenomena*, at once indicates the author's theory that shock is a capillary phenomenon.

The first portion of the book includes an excellent review of capillary structure, physiology, and pathology. This discussion leads to that of inflammation, and from here it is only a step to the exposition of the

TABLE III  
SUMMARY OF EVIDENCE FOR MOON'S HYPOTHESIS:  
"THE WHEAL IS SHOCK IN MINIATURE"

REACTION	WHEAL	SHOCK
Capillaries	Local dilatation	Dilatation in visceral areas
Permeability	Local increase	Increased in visceral areas
Edema	Develops locally	Develops in visceral areas
Stasis	Develops locally	Develops in visceral areas
Capillary hemorrhages	Occur locally	Occur in various tissues
Perspiration	Present locally	Usually profuse

author's theory that a "wheal is shock in miniature." After a discussion of shock, the third part of the book considers various surgical and medical conditions in which a shocklike syndrome may exist. This last, again, is very instructive and valuable from a therapeutic standpoint. In fact, these two peripheral parts of the book are almost indisputable and only the ideas about shock in general are open to question.

Before passing on to a criticism of Moon's theory, it would be wise to state that theory briefly. Moon's definition of shock has already been given. If one phase of it were to be modified, it would be "characterized . . . by increased concentration of the blood." Moon, as will be discussed below, does not believe hemorrhagic shock is typical, and thus excludes it by the above statement. However, changing the word "increased" to "increasing" would allow hemorrhagic shock to be included in the definition (since after bleeding has stopped the blood tends to concentrate if shock is present). The following quotation from Moon's own summary best explains his ideas:

The circulatory deficiencies result from a disparity between the volume of blood and the volume-capacity of the vascular system. The factors in this disparity are: (1) Those which increase the volume-capacity and (2) those which decrease the total volume of blood.

The prime factor causing an *increased capacity*, is dilatation of the capillaries. A large fraction of the total capillary stream bed, which under normal conditions is closed and bloodless, is simultaneously opened to circulation. Not only is the total number of open capillaries raised above normal, their diameters are increased, thus raising their volume content.

Relaxation of sympathetic nerve tonus may be a factor in the capillary dilatation. A more important factor is the direct response of the capillaries to physiologic agents, and to substances of external origin. Much has been said regarding a toxic substance originating in damaged tissues, and extensive chemical and biologic search has been made in efforts to demonstrate and identify it. These efforts have only established and confirmed the fact that in every particular its *physiologic effect* is like that of histamine. Its isolation and chemical identification have not been accomplished.

In this search a consideration of highest significance apparently has been overlooked. Students of capillary physiology have shown, by evidence which has not been disputed, that metabolic substances discharged from tissue cells cause dilatation and increased permeability of the capillary endothelium with which they come in contact. These substances are liberated either by *functional activity* of the cells or by *injury* of any kind to the cells. In the one instance they initiate *functional* hyperemia, in the other, *inflammatory* hyperemia.

This is a physiologic reaction and the agents which activate it should be regarded as belonging to the group of chemical messengers whose importance in the economy of the body is so immeasurable. The accumulation of these substances when the circulation of blood to a large portion of the body is obstructed, or their liberation in excessive amount following extensive injury to tissues, may produce catastrophic effects on the systemic circulation. But such effects are merely an enormous exaggeration of the normal physiologic purpose which those substances serve. To designate these substances as *toxic* requires a broad interpretation of that adjective so that it may include the exaggerated effects of hormonal substances.

Chemical investigations have not yet shown the exact composition of living cytoplasm nor of its derivatives given off during metabolic activity or released by injury. The increase in nitrogenous substances in the blood during shock suggests the presence in excessive amount, of substances derived from cells.

When an increased volume-capacity of the capillary stream bed develops, vaso-motor reactions cause contraction of all the systemic arteries. The large venous channels likewise contract and the peripheral vessels become relatively bloodless. In early stages this is effective in maintaining *undiminished blood pressure*, but it is at the expense of the volume flow of blood. Stagnation and stasis develops [*sic*] in extensive capillary areas, resulting from the combined effects of their complete dilatation and of the decreased volume of fluid.

Frequently the same agent which relaxes the capillary walls renders them abnormally pervious to blood plasma. The leakage of this into the tissue spaces causes the stasis to become permanent, reduces the total blood volume, causes hemoconcentration, reduces the venous pressure and lowers the volume of venous return flow to the heart.

This type of circulatory disturbance develops in varying degrees. The capacity of the circulatory system to re-establish its physiologic equilibrium may be adequate in cases of minor severity. When the volume of blood returned from systemic areas is inadequate the arterial blood pressure declined progressively. This indicates that the mechanism of compensation is failing.

As the volume flow of blood decreases the transportation and distribution of oxygen are correspondingly reduced. The effects of anoxia are then added to the already failing circulation and the self-perpetuating vicious circle is established.

The factors which contribute to the circulatory disparity by *reducing the blood volume* are: loss of blood by hemorrhage, loss of plasma by leakage, and loss of fluid by perspiration, vomiting and diarrhea. Shock seen clinically or produced experimentally usually results from a combination of the factors which increase the capacity of the vascular system with those which reduce the volume of blood.

Shock is defined as a *circulatory deficiency, not cardiac nor vaso-motor in origin, characterized by a decreased volume of blood, reduced cardiac output (volume flow of blood) and by hemoconcentration*. The latter feature appears early, is easily determined and is seen in cases of moderate severity before variations in the blood pressure occur. For these reasons it is useful as an indicator. The following features are regularly associated when the syndrome is fully developed: lowered blood pressure and lowered basal metabolism, diminished renal excretion and usually an increased cardiac rate. In advanced stages the coagulability and the oxygen content of the blood are decreased, the chlorides are below normal, and both the blood sugar and the non-protein nitrogen are increased. Each of these associated features may occur in other conditions but their combination with the circulatory deficiency described completes the syndrome of shock.

A consideration of Moon's book involves two points: First, an estimate of his criticism of other theories; and second, an assay of his own. Considering the first of these, the following points stand out:

1. Moon contends that the bisection type of experiment, as used by Blalock, Phemister, and others, includes a factor of error which was not taken into account. To quote him (page 147): "As fluid escapes from the blood into the tissues of the affected side, fluid is simultaneously absorbed from the tissues of the normal side thereby decreasing its weight. Suppose 100 Gm. of fluid were so shifted: the difference

in weight of the two sides would be 200 Gm., but the *actual gain* of the affected side would be only 100 Gm. The *difference in weight* includes *twice* [italics Moon's] the volume of fluid shifted by dehydration and re-distribution, and such experiments provide no means for determining what amount of fluid is thus shifted. This factor of error, multiplied by 2, occurs in all such computations."

This contention is itself in error in two respects: First, the amount of tissue traumatized or burned is not one entire half of the body, but only about one-sixth. In fact, in Blalock's and Phemister's original experiments the weights of two opposite hind quarters, which represent about one-sixth of the body weight each, were compared. Let us suppose, as does Moon, that 100 Gm. of fluid is shifted into such a traumatized sixth and that it is absorbed from the tissues of the normal five-sixths. Twenty grams of this absorption would be from the opposite hind quarter, so the difference in weight would be 120 Gm. This factor of error of 1.2 is far from that of the 2 cited by Moon and is almost within the limits of experimental error.

Second, there is no real reason for assuming that the fluid lost one place is absorbed elsewhere. As Moon himself says, the "fluid escapes from the blood," and it is an assumption only that it is reabsorbed. Especially is this true when it is remembered that the blood volume in most experiments decreases by almost exactly the amount corresponding to the fluid lost locally, indicating that fluid is *not* "simultaneously absorbed from the tissues of the normal side thereby decreasing its weight."

2. Moon contends that shock and hemorrhage are different. He, like Coonse, Foisie, Robertson, and Aufrane (1935), makes no time classification of hemorrhage in stating this distinction. As pointed out elsewhere, Blalock (1934) showed that, while a rapid hemorrhage either produces death or recovery in most instances, a slow hemorrhage with the blood pressure kept down over a period of hours will give all the signs and symptoms of shock with the typical "wet necropsy" of Moon.

3. Moon states (page 134): "Blalock's sole criterion for shock was a decline in arterial blood pressure." This is quite untrue, as several of Blalock's publications have had as their main thesis that, except as a terminal phenomenon, certain instances of experimental shock are accompanied by practically no decline in blood pressure whatsoever.

In other places Moon criticizes details of the work of those opposing the toxic theory without giving the context of their arguments. Thus, while in certain articles the experiments reported by Blalock were all performed under barbitol anesthesia, in other reports of Blalock ether and other anesthetic agents were used. Therefore, barbitol could not be the cause of shock in all of Blalock's experiments as Moon tends to infer.

The second point in considering Moon's book is his own theory. Much of the evidence for a generalized fluid loss that Moon submits is qualitative. It may be true that in traumatic shock the viscera are engorged, but the important thing is the extent of the engorgement. Furthermore, many of these changes in the viscera are terminal or may be due to anoxia rather than to toxemia. Thus, cause and effect must be carefully differentiated. The views of Blalock are in contradistinction to those of Moon in this regard, as evidenced by the following quotation from the former (1931):

"The main factor which is most likely responsible for the continued low blood pressure after injuries is not a general increase in capillary permeability with loss of fluid all over the body, but a loss of blood plasma through the walls of the damaged capillaries."

Pictures presented in Slome's article (1935), comparing the histology of shock and histamine poisoning, do not agree with those of Moon (1938). Slome showed a congestive picture in histamine shock and a negative one in traumatic shock; Moon showed congestion in histamine and traumatic shock and none in hemorrhagic shock. It is probable that different time factors explained these differences, the two instances of noncongestive picture, one presented by each author, representing acute experiments where there had not been time for stasis to develop.

Then, too, Moon tries to avoid including hemorrhagic shock in his definition. This is not entirely logical and it is certain that there is no color line drawn when the fatal issue is called forth in the animal organism from fluid loss. The fact that some of the lost fluid contains red cells doesn't make it immediately less dangerous; if anything, the opposite is true. But it is just in hemorrhagic shock that the differentiation between initiating factors and perpetuating factors is most easily drawn, and, certainly, toxins or tissue products are *not* initiating factors in hemorrhagic shock. This point will be considered more fully in a separate section on the differentiation between shock and hemorrhage.

On the other hand, Moon's hypothesis explains much of the irreversibility of shock. He shows why shock is fatal and why it is a general body reaction rather than a purely local or local-brain reflex phenomenon. His book is an important landmark in the literature of shock and serves as a point of departure for much new research.

*Scudder's Book.*—The appearance of two books on shock (this and Moon's) within sixteen months is of interest. These two present the problem from quite different angles and it is to be noted that the second (Scudder's) hardly discusses the first at all, the approach being so different. Scudder's book contains more of an exposition of the literature, while Moon's includes a more critical review. Scudder's own thesis is based on three main points as follows:

1. "Blood studies as a guide to therapy." This sentence is a quotation from the title and indicates the importance the author places in these

observations. He makes an especial point of the use of the falling drop method. He thus makes an application of the falling drop method of Barbour and Hamilton (1926) and Kagan (1938) to the shock problem. One of the advantages of this method is that "these four tests [cell volume, specific gravity of whole blood, specific gravity of plasma, and plasma proteins] can be done in 15 minutes time" (page 68), but this statement is hard to correlate with that on the preceding page that centrifuging for an hour is necessary. Furthermore, it seems that the added benefit of this method is purely technical and the same information can be obtained in other ways (viz., Van Allen hematocrits plus direct weight method of determining specific gravity of plasma and plasma proteins, etc.). Thus, Seudder applies a new, and possibly better, method for obtaining information as to the progress of hemoconcentration. He wisely states "that shock can recur despite the correction of oligemia, emphasizes, once again, that hemoconcentration is only one of the many variable factors in shock."

It is noteworthy that Seudder does not place all the emphasis on one aspect of the blood concentration (i.e., relative proportion of cells and serum), but also considers the specific gravity of each separately and the relative protein content as well. Seudder thus considers several variables rather than one and it certainly is true that so complex a mechanism as the mammalian organism has far more than one factor upset under the stress of shock. He states that one advantage of his specific gravity method of following blood concentration is that it is accurate to 10,000 red cells per cubic millimeter; whereas, the ordinary red count is only accurate to 250,000. It is to be noted, however, that the Van Allen hematocrit gives values accurate to 1 part in 45 in a normal blood (about 100,000 red cells). Brown and Clark (1939) found that the use of a graduated pipette and direct weighing gave a more accurate index of the plasma specific gravity than the falling drop apparatus. Bailey (1939) has applied the falling drop method of determining blood concentration to cases of shock associated with nonpenetrating intra-abdominal injury. Although this writer praises the method, he gives no actual data in support of his conclusions.

2. The use of cortical extract. This will be considered under the section on that subject.

3. The increase in plasma potassium accompanying shock. This also will be considered under its appropriate heading.

An appraisal of Seudder's book is difficult until its tenets have stood the test of time. The falling drop method of studying blood concentration is certainly a technical help, even though other methods may give much the same information. The use of cortical extract has been popularized by others, especially Swingle and his co-workers (1933-1938). But the real essential feature of the book is emphasis of the

hyperpotassemia factor. The question now arises: Is hyperpotassemia one of the many *results* (or accompanying factors) of shock that on their discovery seemed so important that they were attributed as being *causes* of shock? There is a long history of such occurrences (acapnia, anoxic degeneration of nerve cells, fat embolism, low blood pressure, etc.) which have upon their discovery been graced with the title causative factor only to be later relegated to the scrap heap of results. This prompts one to consider the above question seriously. This type of reasoning, however, cannot logically exclude the fact that hyperpotassemia may be a very important causative factor in shock. The difference between *initiating* and *perpetuating* factors must also always be kept in mind.

Several of Scudder's conclusions might be worth quoting at this time (the numbers are not Scudder's):

1. Although erythrocyte counts and estimations of hemoglobin are used in measuring hemoconcentration, determination of the specific gravity of peripheral blood is superior because of its accuracy, speed, and greater sensitivity.

2. One common denominator in the phenomena of shock, whether produced by tissue abuse, loss of fluids, hemorrhage, injections of toxins, destruction of the adrenal cortex, or stimulation of the sympathetic nervous system, is a rise in plasma potassium.

3. Heat, adequate fluid administration, and the control of pain are important factors in relieving vasoconstriction, which is undoubtedly also of great importance.

4. The efficacy of transfusion in the treatment of shock is again demonstrated. Better results, however, are obtained by giving both transfusions and salt solutions, since the latter, on the basis of well-established physiologic experiments, probably is of importance in combating the underlying vasoconstriction.

5. To state that shock is due alone to potassium poisoning is fallacious. That alterations in potassium in both the blood and body fluids serve as a measure of profound cellular changes is probably more correct.

## 11. INITIATING FACTORS IN SHOCK

Throughout this discussion, the division into initiating, accompanying, and perpetuating factors is an arbitrary one. In each case there is considerable overlap.

1. LOCAL FLUID LOSS.—As long ago as 1913, Short stated: "The most probable cause of shock, in the writer's opinion, is oligemia, induced by loss of fluid partly into the injured area, and partly through the capillaries all over the body in consequence of reflex vasoconstriction due to stimulation of the pressor afferent nerves." Although over a quarter of a century has passed, this statement is remarkably up to

date. Short also stated that Mummery (1905), Malcolm (1905), Henderson (1908), Roy and Cobbett (no reference given), and even Sherrington and Copeman (1893) believed in transudation giving oligemia.

The classic experiment that so long prejudiced workers against the fluid loss theory can best be referred to after quoting from Cannon's original remarks (1919):

"The development of a low blood-pressure after muscle injury was proved not to be due to loss of blood from the systemic circulation, by carefully skinning the posterior extremities after death, disarticulating the legs at the knees and removing the thighs at the hip by symmetrical cuts through the tissues; the thighs were then weighed. The difference in weight was as low as 11 per cent of the estimated weight of the blood of the animal, an amount which the animal could readily lose without any fall of blood-pressure whatever."

It is to be noted that not only were the subcutaneous tissues—usually an important site of fluid loss—excluded, but also the loose regions of the groin, where most extravasated fluid migrates in such experiments. Furthermore, while the *minimum* of 11 per cent is given, no figures for the *average* are cited. It was only when these experiments were repeated by Blalock and by Phemister that a true idea of the importance of localized fluid loss in traumatic shock was shown quantitatively. This work will now be considered separately.

*The Work of Blalock and of Phemister.*—These two authors and their associates, working independently, are largely responsible for quantitatively showing the importance of local fluid loss in shock. A quotation from Phemister's article in 1928 is the first recorded statement based on experiment of the importance of local loss of fluid into the tissues in the production of secondary traumatic shock:

"Furthermore, necropsy examination of the traumatized limb showed increase in limb volume from hemorrhage which was sufficient to account for the fall in blood pressure. In fact, the volume of blood that it was necessary to withdraw intermittently in the course of an hour in order to kill an animal was always less than the increase in volume of the traumatized limb of the other animal, which was due very largely to hemorrhage in the tissues."

The article by Blalock (1930) entitled "Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury" is certainly one of the most important papers on the subject ever written. Using a higher bisection than Cannon of *hindquarters* rather than below the groin, he found that, when one hindlimb of an animal was traumatized, there *was* enough increase in weight of the traumatized side to cause death. The old Cannon-Bayliss experiments that had concluded that there *was not* enough increase had been performed at the lower level and missed most of the edema that gravitates up into the loose tissue of

the groin. Furthermore, these old experiments were performed comparing the weights of skinned extremities and again much of the edematous tissue must have been removed in the skinning. This paper also contains the following statements that should be reread by later writers who have not correctly quoted Blalock's ideas on the identity of shock and hemorrhage. These are as follows:

"Hence, there may be two types of hemorrhage, that outside the body associated with a dilution of the blood and that into the tissues of the body associated with a concentration. . . . It is believed that these experiments indicate that determinations of the number of red cells and the amount of hemoglobin do not show whether there has or has not been hemorrhage, but rather whether the hemorrhage is outside the body or into its tissues." This last statement, especially, casts doubt on the thesis of those who put so much reliance on the presence of hemoconcentration in deciding their plan of treatment.

Johnson and Blalock (1931) made most important observations on the time relations of the blood pressure fall and the decrease in cardiac output in secondary shock (i.e., following burns, trauma to an extremity, trauma to intestines, and graded hemorrhages) and in histamine shock. The important finding was that the cardiac output dropped appreciably before the blood pressure in the secondary type of shock while the opposite situation held for histamine shock.

In studies on the effect of hemorrhage, Blalock (1934) observed that profound anesthesia by ether or barbital would give hemorrhage into the lumen of the intestinal tract and other tissue changes in control dogs. Using graded hemorrhage, the alterations in the tissues that accompany traumatic shock (the so-called "wet necropsy" of Moon) could be reproduced. Such graded hemorrhages performed under local anesthesia likewise resulted in a "wet necropsy." Blalock further found that even when local anesthesia was used, if the blood pressure was kept at a constant low level for several hours by graded hemorrhages alternating with introduction of more blood, "death occurred in all the experiments, despite the fact that more blood was introduced than was removed." Brooks and Blalock (1934) made observations quite similar to these. In agreement with Blalock (1927), Swingle, Pffner, Vars and Parkins observed (1934) that the slower the bleeding, the greater the quantity of blood which can be removed without symptoms of shock appearing.

In an article appearing two months after Blalock's, Parsons and Phemister (1930) reported work done independently that reached the same conclusions as had Blalock (1930). Also using a higher amputation than Bayliss and Cannon (1919), Parsons and Phemister found that a traumatized limb of a dog is heavier than the corresponding untraumatized limb to an appreciable degree. This increase in weight was considered to be the "predominating factor in the production of the circulatory failure."

This article by Parsons and Phemister and that by Roome, Keith and Phemister (1933) on the effect of bleeding after reduction of the blood pressure by various methods are classics in the study of shock. In the second article it was reported that the bleeding volume, as shown in Table IV, was only slightly reduced in shock due to hyperventilation, anaphylaxis, histamine administration, spinal cord section, and spinal anesthesia. In another type of shock the reduction was marked; namely, following trauma to an extremity, hemorrhage, plasmapheresis, and intestinal manipulation. The shock present in this second type with lowered bleeding volume is what is usually known as secondary shock.

TABLE IV  
BLEEDING VOLUME IN VARIOUS TYPES OF SHOCK\*  
ADOPTED FROM ROOME, KEITH, AND PHEMISTER (1933)

SERIES	PROCEDURE	NO. OF CASES	AVERAGE BLEED- ING VOLUME, PER CENT OF CAL- CULATED BLOOD VOLUME	AVERAGE OF GROUP
1.	Normal dogs	20	58.6	58.6 (Normal)
2.	Hyperventilation	5	56.2	
3.	Anaphylaxis	5	51.0	
4.	Histamine administration	6	50.5	
5.	Spinal cord section	6	48.0	
6.	Spinal anesthesia	6	44.0	
7.	Trauma to an extremity	4	24.6	49.9 (Primary type of shock)
8.	Hemorrhage	7	24.9	
9.	Plasmapheresis	5	19.7	
10.	Intestinal manipulation	6	18.0	21.8 (Secondary type of shock)

\*The bleeding volume is the amount of blood that can be removed after maintaining the blood pressure at a low level by the procedure in question.

Freedlander and Lenhart (1932), by means of standardized trauma to the limbs of cats, confirmed the work of Parsons and Phemister (1930) and of Blalock (1930). In addition, they believed they were able to exclude the possibility of nervous factors. Likewise they compared the amount of blood that could be bled from control cats and found it similar to the amount of extravasation in the traumatized cats. The work of Herbst (1933) on rabbits comes to essentially the same conclusions, although in a later paper (1934) Herbst tends to emphasize nervous factors.

The paper of Phemister and Livingstone (1934) expresses views on primary shock similar to those of Blalock (1934). Emphasizing that "primary and secondary shock should be recognized on the basis of difference in etiology rather than difference in time of occurrence," they point out that most cases of low blood pressure resulting from painful or frightening procedures or from major operations under anesthesia

may be classed as psychogenic or neurogenic in origin. These reactions are essentially reversible and of minor importance.

Beard and Blalock (1931) studied the composition of the fluid that escapes from the blood stream after mild trauma to an extremity, after trauma to the intestines, and after burns. They found the fluid to be comparable to plasma in chloride, sugar, and nonprotein nitrogen and the fluid protein value to be about 80 per cent that of the corresponding plasma. They concluded: "It is believed that the results of these experiments indicate that the loss of plasma proteins is the most important factor in the production of the low blood pressure after the procedures reported." Certainly, this is an important observation, for the mammalian organism can far less easily lose plasma than plain water. Blalock (1934) studied the influence of exposure to cold and of deprivation of food and water on the development of shock. He found that the latter two items had little effect on the resistance to hemorrhage and trauma. However, exposure to cold had a profound influence, depending especially on its duration and the depth of anesthesia.

In secondary shock Blalock (1933) reported a decrease in cardiac output before the blood pressure began to fall. In contradistinction to these results he found that primary shock (the immediate decline following striking the abdomens of anesthetized dogs) was accompanied by an increase in the cardiac output in seven of ten experiments. Furthermore, the oxygen consumption increased during and immediately following the traumatization in nine of ten experiments.

When milder and nonfatal trauma was given in sixteen anesthetized dogs, Blalock (1931) found that the decrease in blood pressure was roughly proportional to the loss of plasma, as evidenced by the difference in weight of the traumatized and the opposite normal limb. Thus:

5 experiments, final mean blood pressure 108 mm. Hg

Difference in weight of limbs averaged 2.41 per cent body weight

10 experiments, final mean blood pressure less than 70 mm. Hg

Difference in weight of limbs averaged 3.66 per cent body weight

Harris and Blalock (1931) found that over a period of hours the muscles of dogs anesthetized with barbital became more dehydrated than experimental animals submitted to trauma under the same anesthesia, although in all cases a slight dehydrating effect occurred. Other contributions of Blalock and of Phemister are considered under their appropriate headings.

Freedlander and Lenhart (1932), as already stated, performed experiments quite similar to those of Parsons and Phemister (1930) and of Blalock (1930). These later experiments compared the shock resulting from trauma to normal cats and to cats with completely denervated limbs. The two series responded in a like manner to the trauma. Furthermore, the amount of fluid and blood recovered in the traumatized

limbs was quite similar in amount to that which produced death of other cats by bleeding. After excluding nervous factors, Freedlander and Lenhart concluded: "The shock following trauma can be explained on the basis of hemorrhage and local fluid loss."

Holt and Macdonald (1934), of Manchester, repeated the work of Phemister and Blalock with confirmatory results. They first did experiments with the blood returning from tranmatized limbs and found on reinjection that the blood always gave a pressor rather than a depressor response. Then in a series of ten dogs with trauma to one extremity and comparison of the weights of the normal and tranmatized limbs, they found the relative increase in weight of the traumatized side to equal 57 per cent of the calculated blood volume (a range of 30 to 83 per cent). This value checks quite closely with those of Blalock and of Phemister. Holt and Macdonald also found that shock developed in other animals following trauma just as readily when the nerve impulses were cut off by spinal anesthesia or when toxin absorption was prevented by common iliac vein occlusion.

The important question arises as to the amount of fluid which, when lost from the blood stream, will produce death. Experimental reports differ somewhat on this score. Boyce, Lampert, and McFetridge (1935) reported that dogs could be bled 4.6 per cent body weight without shock or death resulting. Roome, Keith, and Phemister (1933) reported that 4.5 per cent blood loss would produce death in dogs, and Johnson and Blalock (1931) found the same figure to be 5.1 per cent. Elman and Cole (1934) found that death followed a 2.7 per cent loss of blood from hemorrhage in normal cats. Older observations on the extent of fatal hemorrhage in dogs include those of Béclamp (3 or 4 per cent body weight) and Huenerfauth (3.5 to 4.5 per cent body weight). Evidence obtained from plasmapheresis experiments indicates that experimental animals cannot tolerate the loss of plasma as well as whole blood. These latter experiments are open to the objection that the reinjection of centrifuged cells after the removal of plasma may introduce factors that must be reckoned with besides the plasma loss. The centrifuged cells, even if not hemolyzed, may hasten the occurrence of death in an already weakened animal. Johnson and Blalock (1931) found that dogs would die after loss of varying amounts of blood plasma by plasmapheresis, dependent on the time interval. When the blood plasma was removed in amounts equalling 0.5 per cent weight at hourly intervals, the total amount removed in percentages of body weight varied from 2.5 per cent plasma and 1 per cent whole blood to 3.5 per cent plasma and 0.85 per cent whole blood. The average sum of these figures was 4.05 per cent, which was the average total loss of plasma and whole blood. The figure for the whole blood is necessarily included, because the animals died before the red blood cells from the last bleeding had been replaced.

The average increase in hemoglobin was 34 per cent of the control figures. When the bleedings were performed at six-hour intervals, the average loss was 2.4 per cent plasma and 0.2 per cent whole blood. The sum of these figures is 2.6 per cent, which was the average total loss of plasma and whole blood. The average increase in hemoglobin was 24 per cent of the control figures. Roome, Keith, and Phemister (1933) found that an average plasma loss of 3 per cent body weight in a series of five dogs would reduce the blood pressure to a shock level. These authors found the terminal blood loss in this series to be 1.4 per cent body weight. This makes the total plasma and blood loss 4.4 per cent. The blood was concentrated by this procedure, but no figures in this regard are given in this report. The authors state that removal of less plasma than whole blood would produce death.

Harkins and Harmon (1937) did additional plasmapheresis experiments as shown in Table V, and found that the average amount of plasma which, when removed from experimental animals, will produce death, was 4 per cent body weight. It is noted from the table that the final blood pressure and extent of the hemoglobin and hematocrit rise, as well as the duration of the procedure, are all quite comparable to those occurring in other acute shock experiments.

There seems to be, then, considerable evidence for the importance of local fluid loss being a significant initiating factor in the causation of shock. Robinson and Parsons (1931) have written concerning this concept. Frank (1938) is for local fluid loss and against nervous factors being the cause of shock. Much of the criticism of this theory is based on the misunderstanding that it should explain the whole course of a shock case. Because the diphtheria bacilli do not directly cause terminal myocarditis or tracheal obstruction, we do not argue that they are not the cause of the disease. Similarly, in shock, because a dying patient develops capillary congestion, increased capillary permeability, and breakdown of cell membranes with discharge of cell potassium, this does not argue that the original fluid loss, which precipitated these changes, was not the cause. However, to say that local fluid loss is the only cause or that it acts equally in all types of shock is like riding a good horse to death.

2. SHOULD SHOCK BE DIFFERENTIATED FROM HEMORRHAGE?—Blum (1876) stated that shock is hemorrhage and hemorrhage is shock, and this idea has been popular with some other authors since that time. The association of the two conditions, shock and hemorrhage, in practice is epitomized by the introductory sentence of an article by Erlanger and Gasser (1919): "The injuries that lead to shock in man almost always are accompanied by more or less hemorrhage."

On the other hand, Moon in his book (1938), as already stated above, tries to differentiate between shock and hemorrhage. This idea was

TABLE V  
RESULTS OF PLASMA REMOVAL IN EIGHT ANIMALS  
In Most Instances the Final Blood Pressure, Hemoglobin, and Hematocrit Readings Were Taken Just Before the Final Bleeding

EXP. NO.	BLOOD PRESSURE		HEMOGLOBIN		HEMATOCRIT		DOO WEIGHT KG.	NO. OF BLEEDINGS	INTERVALS IN HOURS FROM FIRST TO LAST BLEEDING	PLASMA REMOVAL PER CENT BODY WEIGHT	BLOOD REMOVED TERMINALLY PER CENT BODY WEIGHT	TOTAL AMOUNT PLASMA PLUS BLOOD REMOVED TERMINALLY PER CENT BODY WEIGHT
	INITIAL	FINAL	INITIAL	FINAL	INITIAL	FINAL						
1	150	56	100	145	53	69	9.3	6	4	3.5	0.0*	3.5
2	120	60	89	148	45	68	9.8	7	9	4.2	0.0	4.2
3	156	70	102	152	44	64	10.4	3	7	3.0	0.8	3.8
4	148	40	77	121	33	56	15.4	7	4½	4.5	0.4	4.9
5	140	48	92	130	62	72	27.0	7	20	3.8	0.5	4.3
6	152	44	106	142	47	66	19.0	7	10	5.6	0.0	5.6
7	146	78	101	168	49	75	13.0	10	10	4.6	0.0	4.6
8	140	68	95	167	57	81	21.5	9	19½	2.8	1.1	3.9
Average	144	58	95	147	49	69	15.8	7	10½	4.0	0.4	4.4

\*In the experiments in which no blood was removed terminally, death occurred between bleedings and after the final red cell reinfusion.

previously presented by Moon and Kennedy (1932) and since has been presented by Moon in a separate article in the *Annals of Surgery* (1939).

Coonse and associates (1935), next to Moon, have been the most ardent recent proponents of the tenet that shock and hemorrhage are different. They stated that traumatic shock is accompanied by acidosis and increased blood concentration, while hemorrhagic shock is not. It is quite true that hemorrhage of sudden onset will have no acidosis immediately, but once depleted of blood the experimental animal will soon develop acidosis. Furthermore, if the hemorrhage is completely arrested, the blood thereafter may become concentrated just as in other shock, especially if the blood loss has been gradual. Later, Coonse and his co-workers admitted that slow hemorrhage simulates traumatic shock. These authors also stated: "Hemolysis has been shown to be consistently present in traumatic shock." "In slow hemorrhage, the findings more nearly resemble those of traumatic shock."

Other authors also try to differentiate shock from hemorrhage. Thus, Mahaffey (1938) listed symptoms diagnostic of hemorrhage—restlessness, anxiety, thirst, and nausea—which are generally recognized as applying equally well to shock. He further stated:

"In hemorrhage, we have a loss of whole blood together with a diminution of the red cell count. In traumatic shock, we have a loss of blood plasma into the injured tissues with a concentration of red blood cells in the circulation."

Hendon (1938) also attempted to differentiate the two, stating: "We do things for shock that we would not do for hemorrhage." He recognized, however, that the two conditions often occur simultaneously. Archibald (1934) also stated in a purely clinical article: "Hemorrhage has nothing to do with pure traumatic shock." This seems to be a rather extreme statement. Furthermore, the remark of Moon that trauma-to-limb experiments are really nothing but instances of hemorrhage is controverted by the fact that Blalock found the hemoglobin content of the fluid expressed from the limb to be only 30 per cent of that obtained from the control. Woodhouse (1940) claimed that bleeding following ruptured ectopic pregnancy is often associated with a slight fever ( $2$  to  $2.5^{\circ}$ ), while shock is not accompanied by fever. This may apply in some cases to hemorrhage into the peritoneal cavity, but certainly not to external bleeding and only occasionally to bleeding into the tissues. An increase in the blood lactic acid after hemorrhage is reported by Riegel (1927). Foote and Gerst (1940) have applied the use of combined specific gravity readings by the falling drop method on whole blood and plasma in the treatment and differentiation of shock and hemorrhage. Leucocytosis in shock and hemorrhage was made the subject of a recent editorial (1940).

Probably the best contradiction of the ideas of Coonse and associates (1935) and Moon (1938) that shock and hemorrhage have little in common and that in the latter there is no general escape of fluids from the blood stream is that of Blalock. This author (1934) pointed out that such a general loss takes place when the blood pressure remains at a low level for several hours. "One rarely encounters in patients, as a result of hemorrhage, a low blood pressure for an extended time. When hemorrhage from a large blood-vessel takes place, usually either the patient dies almost immediately or the remaining volume of blood is augmented by natural or artificial means and the blood-pressure rises." Freeman (1935) also disagreed with Moon and Kennedy's (1932) differentiation of shock from hemorrhage and pointed out again that they did not adequately consider the time factor in hemorrhage experiments.

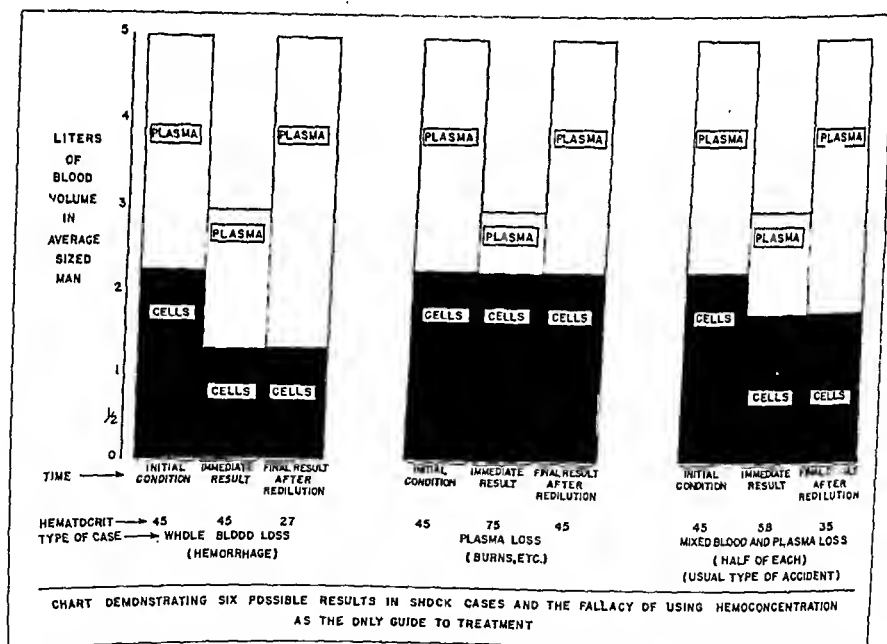


Fig. 1.—Hemoconcentration and shock. This figure demonstrates the variability of the relation between the two.

In experiments on shock produced in two ways, (1) repeated trauma to both hindlimbs and (2) repeated hemorrhage, Davis (1937) attempted to show if shock produced by trauma was similar to that produced by hemorrhage as evidenced by the histopathologic changes. The results indicated no essential difference. In both instances there was a variable amount of blood-stained, plasmalike peritoneal fluid, the intestines were relaxed and flabby, and constriction of the arteries was present. No

evidences of splanchnic congestion were found. The lungs were edematous to a degree, depending on the duration of the shock state, and the heart was diminished in size proportional to the decrease in blood volume at the time of death. Davis concluded: "It may be stated that the histopathologic appearance is the same both in traumatic and hemorrhagic shock, which suggests that the basic etiology is similar."

It would seem that from the practical standpoint alone, a differentiation between hemorrhagic and other types of shock is disadvantageous. In clinical cases usually both whole blood and plasma are lost. A patient suffering from shock, who has lost a little whole blood in addition, is just as deserving of shock treatment as a simpler case. After all, it matters little what color fluid is lost from the blood stream, red or yellow. The numerous possible combinations of blood concentration after complicated injuries are shown in Fig. 1.

### III. ACCOMPANYING FACTORS IN SHOCK

A number of changes occur in shock that are common to most types. Many of these may be initiating or perpetuating factors as well, but at least their presence is common and they are present through most of the course of shock. Hence, they will be considered at this point. Reference should be made to Table VI. If the causal relation is to be emphasized,

TABLE VI

#### HISTORICAL DEVELOPMENT OF EVIDENCE FOR CERTAIN FEATURES OF SHOCK\*

1. <i>Oligemia</i>	2. <i>Decreased cardiac output</i>
Short, 1913 Mann, 1915 Robertson and Bock, 1918 Keith, 1919 Gasser, Erlanger, and Meek, 1919 Gesell, 1919 Phemister, 1930 Blalock, 1930 Freedlander and Lenhart, 1932 Holt and Macdonald, 1934 O'Shaughnessy and Slome, 1935	Boise, 1907 Henderson, 1908 Markwalder and Starling, 1913-1914 Wiggers, 1918 Blalock, 1931
3. <i>Vasoconstriction</i>	4. <i>Vasomotor center intact</i>
Lister, 1858 Mapother, 1879 Malcolm, 1893 Skeen, 1906 Gray and Parsons, 1912 Short, 1913 Pilcher and Sollmann, 1914 Freeman, 1935	Porter, 1907-1908 Seelig and Lyon, 1910 Mann, 1914 Wiggers, 1914 Pilcher and Sollmann, 1914 Cattell, 1922
5. <i>Decreased blood flow</i>	
Morison and Hooker, 1915 Gesell, 1917-1918 Erlanger and Gasser, 1919 Aub and Cunningham, 1920 Freeman, 1935	

\*These lists are not exhaustive.

these factors might be called "sustaining factors" as well as "accompanying factors."

1. *Oligemia*.—This is undoubtedly one of the most important changes occurring in shock. Erlanger, Gesell, and Gasser (1919) had early demonstrated an increase in the peripheral vascular tone in experimental shock. Gesell (1919) found that a decrease in blood volume of less than 10 per cent produced by hemorrhage may cause a decreased blood flow through the submaxillary gland of more than 60 per cent even though accompanied by a rise in general arterial blood pressure. Roome, Keith, and Phemister (1933) noted a low "bleeding volume" in hemorrhagic and traumatic shock and a near normal one in histamine shock. Using the carbon monoxide method, Aikawa (1935) found the decrease in blood volume accompanying surgical operations on dogs to average 18 per cent with many values showing more than 30 per cent decrease. Since many of these operations were minor, the decrease in shock-producing procedures should average considerably more. Derra (1937) showed a reduction in blood volume accompanying anesthesia.

Derra (1936) used a combination of the carbon monoxide and dye methods in studying blood volume changes in dogs under avertin anesthesia and observed both increases and decreases, the range being from plus 45 per cent to minus 28 per cent of the preoperative values. He observed that during laparotomies the plasma volume tended to fall and the cell volume to rise with decrease in the total volume. More recently Gibson and Branch (1937), of Boston, did blood volume studies on twelve surgical patients by the Evans blue dye method. They found that the total volume is reduced at the end of the operation, the reduction being due to a diminution of plasma volume larger than can be offset by influx of red cells into the circulation. None of their patients were in a condition of shock, the blood pressure being well maintained throughout, and apparently no great external loss of blood occurred. Neuwelt (1939) found the vital red dye method for determining blood volume accurate for normal dogs but inaccurate in dogs in shock. He also found that splenectomy produces a decrease in circulating blood volume and that such animals develop shock more easily than normal dogs.

The new studies of Gibson and Evans (1937), Gibson and Branch (1937), Gibson, Keeley, and Pijoan (1938), Gibson and Evelyn (1938), Gregersen, McAllister, Pinkston, and their associates (1935-1938), and Gregersen and Stewart (1939) on blood volume by means of the use of the Evans blue dye (T-1824) have opened up a new field. This method, using either a spectrophotometer or photoelectric colorimeter, has made the determination of blood volume much more accurate than any previous method. This new procedure has once again confirmed the observation that oligemia accompanies shock.

2. *Diminished Blood Flow.*—It is a common observation in both patients and experimental animals with shock that the peripheral blood flow is decreased. Thus, there is great difficulty in obtaining (or administering, because of difficulty in doing a venipuncture) blood from superficial veins or from ear or finger punctures in severe shock. More quantitative evidence of this decrease in peripheral blood flow was obtained by Freeman, Shaw, and Snyder (1936), who found that the blood flow through the hand is markedly reduced in shock patients.

The importance of reduction of blood flow was early recognized by Gesell and Moyle (1922), who found a decrease in the volume flow of blood through the striated muscle of dogs after hemorrhage. In a series of hemorrhages in the same animal, the late ones invariably produced the greatest reduction in blood flow. Injections of gum saline solution produced an increase in volume flow out of proportion to the increase in blood volume. In a later paper (1922) these authors reported a decreased response to electrical stimuli associated with the decreased volume flow in muscles. They discussed the relation of this change to nutrition of the tissues and in turn the role played by these factors in shock.

More recent observations on this point include those of Meek (1936), Freeman, Shaffer, Schechter, and Holling (1938), Roome (1938, 1939), and others. Klemperer, Penner, and Bernheim (1940) believe that the intestinal lesions present in shock are due to spasm of the vessels. Further studies on the general subject of blood flow through the dog's paw were made by Freeman and Zeller (1937). Cammer and Griffith (1939) showed that the intra-arterial injection of adrenalin reduces the blood flow and  $O_2$  consumption of the intact hindlimb of the cat. The recent observations of Roome (1938) on the effect of intra-arterial epinephrine on the blood flow in an extremity are of great fundamental importance. This author, using his own photoelectric modification of the Ludwig Stromuhr, injected small doses of epinephrine into the femoral artery of dogs. The typical response seemed to be a dilatation of the capillaries and a constriction of the arterioles and arteries in the muscles. Roome (1939) found a marked diminution in the peripheral blood flow to occur in dogs with only moderate hemorrhage. He concluded that this lent "support to the ischemic theory of shock."

Blalock and Levy (1937) studied the blood flow through the posterior part of the body, the kidneys, the portal system, and the anterior extremities and head before and after (a) hemorrhage, (b) intestinal trauma, and (c) histamine administration. Hemorrhage and intestinal trauma were accompanied by a greater diminution in the flow of blood through the posterior part of the body and a smaller decrease elsewhere. Histamine, on the other hand, was usually associated with a general reduction in the flow of blood throughout the body. This once

again confirms the opinion that histamine and traumatic shock are different. It is to be remembered that Johnson and Blalock (1931) showed that in hemorrhagic and traumatic shock the cardiac output declines first; whereas, in histamine shock the blood pressure falls first.

All of these writers obtained confirmatory results and it seems to be without question that a decrease in blood flow is one of the prime factors in shock. So important and progressive is it that one might almost say that to diagnose shock a lancet to cut the ear or finger and determine the blood flow would prove almost as useful as all the sphygmomanometers ever made. If one were to select a single determination to follow the course of shock, an observation of the peripheral blood flow might be the best to choose.

3. *Inadequacy of Fall in Blood Pressure in the Diagnosis of Shock.*—It has already been mentioned that in secondary shock a fall in blood pressure is often a terminal phenomenon occurring long after marked hemoconcentration and decreased blood flow have become evident. We have indeed come a long way from the belief implied in the statement of Rowell speaking before the annual meeting of the British Medical Association in 1910 that: "A falling blood pressure is the first sign of the onset of shock." A more modern opinion is that expressed by Blalock (1927): "The blood pressure is an inadequate guide to the state of the circulation in incipient shock."

Older observers had noted that there were marked changes in the circulation before a shock level of blood pressure was approached. Gesell (1919) showed a slowing of blood flow through the salivary gland before a fall in pressure occurred. Henderson (1909), in working on shock produced by intestinal trauma in dogs, found a markedly decreased oxygen content of venous blood. In severe anemia the oxygen content of venous blood may be as low as in shock, but that of arterial blood is likewise reduced as shown by Aub (1920). The conclusions of this latter author are worth listing:

1. There is a markedly diminished oxygen content of the venous blood in experimental traumatic shock. This change occurs before the blood pressure falls to a shock level and is still present after apparent recovery from shock.

2. The blood flow is also greatly decreased in the development of, during, and after shock.

3. The resulting anoxemia of the tissues may be the cause of the decreased metabolism.

4. *Acapnia.*—The idea that the acapnia which accompanies shock might be a causative factor was introduced by Henderson (1908). This was partly based on experiments on the production of shock by overbreathing alone. Janeway and Ewing (1914) showed that, while artificial respiration when rapidly given leads to acapnia and shock,

when carbon dioxide is given at the same time and there is no acapnia, shock develops anyway. These authors believed that this shock was the result of increased intrabronchial pressure and not of acapnia. It thus seems that acapnia is a result rather than a cause in most types of shock. Milroy (1917) showed that there is a low alkali reserve after hemorrhage. Further observations on acapnia and blood volume were made by Henderson (1930) and Rühl (1938). Seevers and associates (1939) presented data which, when compared with the effects of voluntary hyperpnea in man and correlated with the results of animal

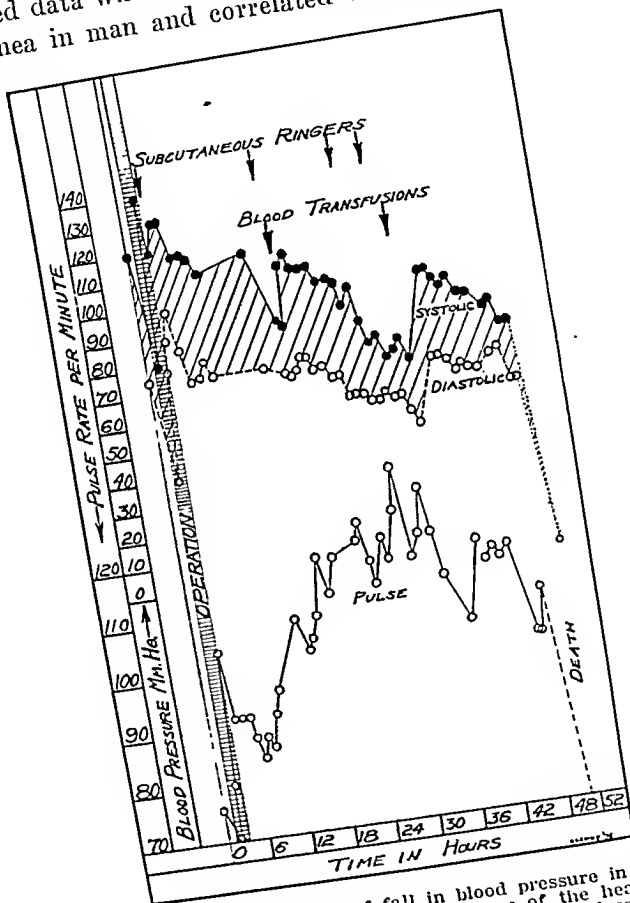


Fig. 2.—Inadequacy of observation of fall in blood pressure in diagnosis of shock due to hemorrhage. In this patient with malignancy of the head of the pancreas, marked jaundice, and postoperative bleeding into the peritoneal cavity, treated before the days of vitamin K, it is seen that the fall in blood pressure was not a perfect guide as to the seriousness of the condition until shortly before death. The increase in pulse rate was a much better guide early, but its late improvement was deceiving.

experiments, show that the arterial hypotension due to the rapid removal of carbon dioxide is a phenomenon which obtains only during anesthesia. They believe it is incorrect to classify this hypotension as surgical shock, since (1) the hypotension is not progressive, (2) recovery of arterial pressure occurs even during continued ventilation, and (3) when hyperventilation is discontinued, recovery is immediate.

Associated with or related to the acapnia is often an *acidosis*. Hertzman and Gesell (1926) showed that following hemorrhage there is an increased acidity of the venous blood. Because of this acidosis, Cannon (1918), Coonse and co-workers (1935), and others advised intravenous sodium bicarbonate in shock cases. It now seems that acidosis is not a causative factor in shock and there is no basis for treating it at present. The underlying anoxia is probably much more important.

5. *Decreased Muscle Tonus*.—The possibility that muscle tonus may be of importance in helping the venous return of blood to the heart, and hence in maintaining an adequate cardiac output, has been discussed by Henderson (1931, 1938, 1939), Henderson, Oughterson, Greenberg, and Searle (1934, 1936) and Beigelböck and Steinlechner (1938). Ornstein, Licht, and Herman (1939) have suggested that, if low muscle tonus is a factor in shock, faradic stimulation of muscles might be of help. They found that such stimulation increases the muscle tonus and at the same time raises the venous pressure.

6. *Decrease in Venous Pressure*.—Certain older writers, including Crile (1899), Sheen (1906), and Penfield (1919), reported an elevated venous pressure in shock. Possibly because certain of their readings were made in the portal system these results are not in agreement with modern studies which show almost unanimously that the general venous pressure is decreased in shock. They include the observations of Morison and Hooker (1915), Wiggers (1918), Henderson (1931), and Ornstein, Licht, and Herman (1939). Wiggers (1918) stated in this regard: "The decreased venous pressure and consequent reduction in minute output is the predominate factor in the pronounced fall of arterial pressure during the progressive stage of shock." His next statement in the same article would not bear up so well under modern scrutiny, however, if the work of Freeman (1933), is to be considered, for Wiggers attributed the initiating factor to be a "reduction in peripheral arterial resistance."

Other important accompanying factors in shock are merely listed here because they are discussed elsewhere in this paper. In many cases these are of just as much or more importance as those more fully discussed above, and the discrimination is in other ways entirely arbitrary.

7. *Hemoconcentration* (see Initiating Factors).
8. *Decreased Cardiac Output* (see Initiating Factors).
9. *Vasoconstriction* (see Adrenal Medulla).
10. *Decreased Metabolism* (see Anoxia).
11. *Capillary Congestion* (see Histamine).

*Miscellaneous Experimental Studies*.—Many of these, having important bearing on the shock problem as a whole, are presented here, rather than under separate headings as are other studies. The fundamental work of Swindle, of Milwaukee (1936), on the perivascular

seep valves and their relation to the exchange of body fluids has an important bearing on this aspect of the shock problem. The work done in Krogh and Rehberg's laboratory by Asmussen, Christensen, and Nielson (1939) on the relation of posture to circulation has an affiliation to the shock problem. Other interesting studies include those of Fåhræus (1931), who showed that below a critical point of about 0.3 mm. for the diameter of a tube blood does not obey the law of Poiseuille, but actually has less viscosity than would be so if it were a homogeneous liquid. These studies have an applicability to the flow of blood in arterioles in shock.

The studies of Adolph, Gerbasi, and Lepore (1933, 1934) on fluid redistribution after hemorrhage and transfusion are of interest. They found that the dilution of the plasma following hemorrhage, and presumably due to influx of tissue fluids, requires about twenty-two minutes for its approximate completion. Following transfusions and other infusions, the redistribution of fluid was also quite rapid. Davis and Jernstad (1939) performed experiments to study the regional redistribution of blood in experimental secondary shock. Anesthetized animals were placed on a platform and the relative weights of the head, thoracic, splanchnic, and hindlimb regions determined serially. There was a similarity in the regional redistribution of blood after hemorrhage and that after trauma. A shift from the splanchnic area occurred with early increase in the blood in the thoracic area followed by a decrease. A late increase in the blood in the extremity areas occurred. The authors concluded from this experiment, which is rather elaborate and technically difficult to interpret, that "direct experimental evidence is offered against the occurrence of a splanchnic 'pooling' of blood in traumatic and hemorrhagic shock."

Davis (1937) performed another interesting series of experiments to test the theory of "splanchnic pooling" of blood in shock. These experiments attempted to determine quantitatively the regional redistribution of blood in the intact animal in a state of shock. By the use of a specially designed apparatus, the head, thoracic, abdominal, and peripheral (hindlimb) areas of nembutalized dogs were weighed before and during the production of secondary shock. It was found that trauma is associated with a loss of bloody fluid into the traumatized area. Simultaneously blood is lost from the cephalic, splanchnic, and thoracic regions, except in very long experiments where a secondary increase in weight of the thoracic area takes place as a result of edema of the lungs. In hemorrhagic shock the greatest loss is from the splanchnic area and to a lesser extent from the thoracic and cephalic regions. In histamine shock blood is shifted into the thoracic and abdominal areas. These findings do not provide any evidence for

splanchnic pooling in traumatic or hemorrhagic shock but furnish differentiation of histamine shock from shock of traumatic or hemorrhagic origin.

The experiments of Doménech-Alsina and his associates of Barcelona (1933) are of great interest. These experiments revealed that shock could be produced by irrigating the peritoneal cavity with hypertonic solutions. The following irrigations were performed:

1. Hypertonic saline solution (40:1,000) gave a progressive blood pressure fall, with a decrease in the carbon dioxide reserve and an increase in the hemoglobin and chlorides in the blood. Sometimes the blood pressure fell suddenly at the end of the experiment after being relatively well maintained hitherto.

2. Isotonic saline solution (7:1,000) gave no blood pressure change or slight fall, no change in hemoglobin or chlorides, decrease in carbon dioxide reserve.

3. Hypotonic saline solution (3:1,000) gave no change in blood pressure or carbon dioxide reserve, slight increase in hemoglobin, decrease in chlorides and glucose.

In these experiments it was found that adrenalectomized dogs died more quickly than the control animals. Experiments somewhat similar to those of Doménech-Alsina were performed by Curtis and by Davis, Hauke, and Curtis (1930). These authors perfused the peritoneal cavity of rabbits with distilled water and produced a marked hypochloremia. The experiments of Curtis and Huggins (1928) indicate that even normal saline solution will irritate the peritoneum of rabbits.

#### IV. IRREVERSIBILITY OF THE SHOCK SYNDROME

One of the most interesting features of shock is that after it has existed a certain time measures that would have led to recovery in the early stages are of no avail. This irreversibility exists in shock due to trauma, burns, and other injuries. The experiments of Pileher and Solhmann (1914) indicate that shock from hemorrhage is also irreversible. These authors found that as dogs are bled, if the blood is reinjected during an early stage of the process, recovery is possible, but later blood pressure "can only be brought back to 60 mm., no matter how much fluid is injected." Blalock (1934) came to similar conclusions with regard to hemorrhage.

Cannon (1919) gave a discussion of the vicious circles in shock. Fantus (1938) is another who recognized the irreversibility of the shock syndrome. While shock is undoubtedly irreversible in its later stages, it is not so much so as inferred by O'Shaughnessy and Slome's statement (1935) as follows: "It has been our experience that the subject of severe trauma who does not show some signs of recovery under established modes of treatment within two or three hours of his injury is almost inevitably doomed." A case of mine<sup>333</sup> is at least one

exception to this rule. This may, however, merely be another bit of evidence for the fallibility of blood pressure readings in shock prognosis.

As to the cause of the irreversibility in shock, search must be made for some perpetuating factor or factors. It is certain that in the late stages of shock there is a *generalized* increase in capillary permeability. Bell, Clark, and Cuthbertson (1938) believed that a generalized fluid loss plays some role in traumatic shock. This generalized fluid loss may result from or be associated with one or more of the following factors. It is to be remembered in each case, however, that these may not be causative agents, but merely evidences of general cell injury. Even the increased capillary permeability may not be a causative but merely an associated change.

#### POSSIBLE PERPETUATING FACTORS IN SHOCK

1. Anoxia
2. Hyperpotassemia
3. Adrenal medullary overaction
4. Adrenal cortical insufficiency
5. Histamine or other tissue metabolites
6. Nervous factors

1. ANOXIA.—The importance of anoxia in shock has been recognized for some time and Cannon in his book (1923) devotes considerable attention to it. That its importance continued to be recognized considerably more recently is evidenced by a quotation from the next book on shock (Moon's) appearing in 1938: "Anoxia probably is the most important factor tending to increase or perpetuate the circulatory deficiency." Krogh, as early as 1922, recognized the vicious circle in shock and the possible role of anoxia in it, stating:

"A very essential feature in the aetiology of shock is the vicious circle, which is set up by the poisoning of the capillaries. When the circulation begins to fail the blood supply to the tissues suffers and this in turn leads, by reason of oxygen lack or by reason of the diminished supply of tonic hormone, to still further dilatation. At more advanced stages the permeability of the capillary wall is so far increased that loss of plasma occurs, thus aggravating once more the failure of the circulation."

One could go even further back to find references to anoxia. Moon (1938) states that John Hunter advised oxygen in the treatment of shock. Professor Leonard Hill of London (1910), who believed shock was caused by "a paralysis of the synapses by a widespread injury which caused a defective transmission at these points," was an early advocate of the administration of oxygen to shock cases. The object was to "maintain the circulation which would allow the synapses to

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The work of Courville (1936) on the anoxic changes in the brain following nitrous oxide anesthesia led to renewed interest in the importance of anesthesia in shock. The following quotation from Courville's article is of interest:

"As a rule these patients developed respiratory or cardiorespiratory failure while under nitrous oxide-oxygen anesthesia and failed to regain consciousness when the anesthetic was withdrawn. During the survival period the patients remained in coma, frequently had convulsions and most of them died in a state of hyperthermia after an interval of  $1\frac{1}{2}$  to 26 days. A few individuals recovered, some with a residual lenticular syndrome, others with a permanent psychosis, while some fortunately recovered completely. In the fatal cases the cerebral cortex and the lenticular nuclei presented areas of necrosis which at times became confluent and if the survival period was sufficiently long, resulted in astrovascular scars."

McClure, Hartman and their associates (1939) extended these studies to cover the effects of most of the present-day anesthetics and the various premedications used with them. These authors also did numerous blood oxygen tests on human beings under anesthesia and on experimental animals. They found that evipal and other barbiturates in full doses were especially culpable, and that in large doses morphine was as well. This latter point is of especial interest to the whole shock problem, since morphine is so widely used as a means of shock treatment. This use, largely empirical, is chiefly a result of the imputations of the older nervous therapy of shock. Possibly quantitative experimental studies may prove this empiricism in error.

Davis (1937) decided to make metabolic determinations by means of a Krogh respiratory apparatus to follow the rate of oxygen consumption in secondary shock. In normal dogs it was found that the intravenous injection of normal salt solution increased the rate of oxygen consumption by 25 to 50 per cent. The maximal increase followed the introduction of 1,400 to 2,400 c.c., and with more solution a plateau in the curve is maintained. The tolerance for water was found to be great in normal animals, and up to 25 per cent body weight of normal saline solution could be given without deleterious effects. Davis found that in traumatic and hemorrhagic shock, on the other hand, a peculiar alteration of the metabolic response to fluids occurs. The maximal increase in the rate of oxygen usage is reached at an earlier stage of the fluid injection; i.e., after 700 to 1,200 c.c. of the fluid have been given. Further administration results in a progressive decline in the rate of oxygen consumption, only 5 to 12 per cent body weight of fluid producing a fall in the metabolic rate. Along with these metabolic changes in secondary shock, there is a marked alteration in renal function, the water diuresis being minimal even after large infusions.

recover." Bayliss (1918) realized the importance of anoxia in shock, stating: "At the risk of tiresome iteration, I would again emphasize the importance of adequate oxygen supply to the tissues."

Landis (1928) studied the effects upon capillary permeability of oxygen lack, of high tensions of carbon dioxide, and of increased hydrogen-ion concentration as observed in single capillaries of the frog mesentery. Direct measurements of fluid movement in cubic micra per square micron of capillary wall per second was correlated with the capillary pressure. After a three-minute period of oxygen lack, fluid filtered through the capillary wall at approximately four times the control rate. The increased permeability of the wall permitted also the passage of protein and thus reduced the effective osmotic pressure of the plasma proteins to almost one-half their normal value.

This fluid movement through the asphyxiated capillary wall was directly proportional to the difference between capillary pressure and the effective osmotic pressure of the plasma proteins, indicating that the wall, although more permeable than normal, still acted as a passive filter. When normal circulation was restored, the capillary wall soon recovered its impermeability to protein and the rate of fluid transudation was also reduced almost to normal.

The effect of carbon dioxide was only slight, even complete saturation of the perfusing fluid increasing transudation only slightly, and the wall remained normally impermeable to protein. Increase in hydrogen ion concentration within normal limits had little or no effect, though at pH 4 the characteristic effects of injury appeared.

The whole question of anoxia has been further developed by the important work of McClure, Hartman, and their associates (1935-1939). These authors first investigated the effects of artificial fever therapy. The pathologic changes resulting from this treatment in both human cases and experimental animals were engorgement of the blood vessels, especially the capillaries, and hemorrhage and cellular degeneration. The most marked changes occurred in the brain, lungs, and adrenals, with hemorrhagic encephalitis, hemorrhagic pneumonia, and hemorrhagic degeneration of the cortex respectively. Death occurred from vascular collapse. Chemical analysis revealed that these changes were closely related to the development of anoxia. The combination of depressing action of sedatives, such as sodium amytal, usually given to fever therapy cases, with the increased demands for oxygen due to the increased metabolism associated with the hyperpyrexia, exaggerated any other factors decreasing the oxygen supply.

The pathologic changes were similar to those of anoxia produced in other ways. They could be prevented by the administration of oxygen throughout the fever treatment, provided respiration and blood pressure were maintained at reasonable levels.

Freeman, Shaw, and Snyder (1936) found that not only was the blood flow through the hand in clinical cases of shock markedly reduced, but also that the low oxygen saturation of the venous blood indicated the severity of the tissue asphyxia. Tomb (1937), on the basis of Freeman's previous work, advised ergotoxine to relax the sympathetic nervous system plus oxygen inhalations in the treatment of shock. He stated: "All the symptoms of shock are directly referable [sic] to over stimulation of the sympathetic nervous system, and to consequent asphyxiation of the cells of the body through want of oxygen."

In experiments on dogs Wood, Mason, and Blalock (1940) studied the effects of inhalation of a high concentration of oxygen in shock. Shock was produced in three ways (hemorrhage, histamine, and trauma) and blood oxygen utilization studies were made by studying the oxygen content of the femoral, renal, and portal veins and of the venous blood from the whole body in the right heart. The inhalation of oxygen under these conditions resulted in a considerable increase in the amount of oxygen available to the tissues, as evidenced by a rise in arterial oxygen content and increases in the venous oxygen content of blood from the various sources listed above. This availability was possibly further enhanced by concomitant increases in carbon dioxide tension in consequence of the so-called Bohr effect (raised carbon dioxide tension increases the percentage of oxyhemoglobin dissociated at a given oxygen tension). Wood, Mason, and Blalock concluded that their results indicated that inhalations of high concentrations of oxygen exert a beneficial effect in the treatment of peripheral circulatory failure.

Another direction in which oxygen therapy has been advanced is the use of high concentrations (80 to 90 per cent) of oxygen, as with the B.L.B. mask. This relieves the tissue anoxia present in so many cases. It is to be remembered that in many cases of shock accessory injuries impede oxygen intake as well as oxygen transport in the blood. Davis (1940), in a study of fifty necropsies following shock, emphasized the importance of anoxemia of the central nervous system. Varangot (1940) stated: "*Le blessé choqué meurt d'anoxémie.*"

Tannenbergh (1939) has recently studied the pathologic effects of anoxia and insulin shock in rabbits. He found the effects of the two quite similar with definite cerebral changes somewhat reminiscent of Crile's "exhaustion" effects and changes in the cardiac muscle and liver. In the latter organ hydropic changes of hepatic cells were observed with occasionally definite focal necroses. The similarity of these changes to those occurring in burns is to be noted. Keeley, Gibson, and Pijoan (1939) found that in experimental burn shock the oxygen saturation of venous blood was reduced in all animals. The

Davis called this diminution of oxygen usage after fluid administration in secondary shock the "anoxemic response" and believed it may be due to one of three factors: (1) insufficiency of oxygen available in lungs; (2) decrease of oxygen-carrying capacity of the blood stream; and (3) interference with oxygen utilization by the tissues.

He ruled out the third factor by showing that in normal animals excess fluid administration even to the point of edema caused no decrease in oxygen consumption. Furthermore, the pulmonary edema did not seem to be the cause of the anoxemia, although Davis did not give detailed data in this regard. He concluded in favor of the second factor, saying: "It is suggested, therefore, that the augmentation of the anoxemia of shock by fluids is the result of loss of protein and cells into the traumatized area, the peritoneal cavity and to a lesser extent into the alveoli of the lungs and general tissue spaces." It is difficult to follow the reasoning here as the plasma protein, which is washed out, is of relatively slight importance as a carrier of oxygen in comparison with the hemoglobin.

Other workers have emphasized anoxia. Thus, Andrews (1935) pointed out the danger of anoxemia during surgical operations and attributed some cases of shock to it. Meek (1936) also realized the importance of anoxia in shock, stating that shock is followed by a set of pathologic-physiologic reactions and "the most important of these are the production of tissue anoxemia and increased capillary permeability."

It might be mentioned parenthetically at this point that use of the term "anoxia," as adopted by Hartman, is preferable to "anoxemia" except in cases where one is referring specifically to blood.

Anoxia in shock was studied by Mertens (1938) and Schwarz and Malikiosis (1938) in Germany. The observations of Kabat and Dennis (1938, 1939) and Dennis and Kabat (1939) on cerebral anemia indicate the importance of anoxia, but the animals did not develop a shock-like condition. This indicates that anoxia of the brain alone may not be a prime factor in producing irreversible shock. The importance of anoxia might be further exemplified by a quotation from Moon (1938): "So far as the actual mechanism is concerned, many phenomena called toxic are essentially anoxic." Crile's findings of degenerative changes in the central nervous system accompanying shock are explained on an anoxic basis by Moon (1938): "It is probable that the changes described are due to anoxemia and are the result rather than, as Crile supposed, the cause of shock." (Possibly this confusion of cause and result might be turned about towards some of the theories of Moon himself.) Sheehan (1940) reported a series of fatal cases of shock with subendocardial hemorrhages as a frequent finding. He stated that he believed they appeared too old to be due to terminal anoxia.

at death was 29.8 mg. per cent. These authors concluded, therefore, that the human cardiac muscle is more susceptible to potassium than that of certain other animals. This conclusion is true, of course, only if the hyperkalemia was the cause of death, but the authors do not state that.

More recently, Scudder, Corcoran, and Drew (1940) have extended the observations on the increase in serum potassium to cadaver blood. In twenty-seven cases the average concentration of the serum potassium was 101 mg. per cent. This high value is approximately 3.5 times the concentration found at death and nearly 6 times normal values. Experiments indicated that ammonia production might be responsible for this rapid diffusion of potassium from the cells into the serum. Furthermore, it was believed that the diffusion was accelerated by the fact that the cadavers were not placed immediately in a refrigerator. The writer spent two days in Youdine's laboratory and learned the type of case that Youdine used for obtaining cadaver blood. Only one of Scudder and his co-workers' twenty-seven cases would strictly come under this head; namely, a case of multiple fractures of the skull with a serum potassium of 72. Since this reading is elevated, although not as markedly as the average of the others, Scudder's point is not much weakened. Drew, Edsall, and Scudder (1939) have recently reported that, while there is little loss of red cells over a period of thirty days in heparinized blood, the plasma potassium content increases tenfold.

De Gowin, Harris, and Plass (1940) found that during blood storage, the potassium of the erythrocytes diffused into the plasma where it attained a maximum concentration in two weeks. Transfusion into human beings of blood with maximum plasma potassium was accompanied by no clinical, chemical, or electrocardiographic evidence of toxicity. It is to be remembered, however, before applying this dictum too literally that there is enough potassium in 3 liters of blood to cause death. Therefore, avoid transfusion of preserved blood in large amounts.

Zwemer and Scudder (1937) produced shock in cats by extensive crushing of tissue, intestinal manipulation, acute pancreatitis, intestinal obstruction, and hemorrhage. These animals developed blood potassium levels similar to those found in animals with severe adrenal insufficiency or shocked by intraperitoneal injections of potassium salts. Rises of 50 to 100 per cent were not uncommon and high potassium levels were also found in the fluids obtained from closed body cavities. These authors concluded on the basis of the findings:

"Since the effect of excess potassium in extracellular body fluids is in many respects similar to that of histamine, and as injections of histamine are followed by increased blood potassium (Thaler), our

values dropped to less than 10 per cent prior to peripheral collapse in those animals that succumbed. Ziegler and associates (1940) have recently reported that partial anoxia in dogs, produced by breathing an atmosphere containing 5 per cent oxygen, leads to a fairly marked decrease in plasma potassium.

*Decreased Oxygen Consumption.*—Some of the early work of Aub (1920) and others on the decreased metabolism in shock indicated a decreased oxygen consumption. Gesell, Blair, and Trotter (1922) found the oxygen consumption in dogs immediately following hemorrhage to be 29 per cent below the control figure. Bearing on the question of anoxia are the experiments of Schlomovitz, Ronzone, and Schlomovitz (1924), who studied experimentally the oxygen consumption during repeated slight bleeding. At first there was little change, but after about 1.5 to 2.5 per cent body weight was removed by bleeding, a marked decrease in oxygen consumption occurred. Related to the decrease in oxygen consumption and decreased metabolism, there is a fall in body temperature accompanying shock. Kinuaman (1903) stated in this regard: "As shock increases in severity, the most uniform and progressive factor is the fall in temperature." Other studies on the oxygen consumption include those of Schneider (1938) and Bansi (1938) in Germany and Davis (1936, 1937) in this country. Davis found a decreased metabolism and concluded (1936) that "shock is accompanied by a marked fall in the rate of oxygen consumption." It will be mentioned again in conclusion that the classification of anoxia as a perpetuating factor in shock is somewhat arbitrary. It certainly is to some extent an accompanying factor as well.

2. *HYPERPOTASSEMIA.*—The importance of hyperpotassemia has been re-emphasized by the recent studies of Scudder and his associates. Potassium is of importance not only in the body of the victim of shock, but also in the blood that he may receive during treatment. It thus has a dual importance and deserves attention at this time. That potassium changes are not an important initiating factor in shock is indicated by the lateness of their onset. They seem to be associated with general cell damage and may thus be either merely an accompanying or actually a perpetuating factor in shock.

The observations of Scudder, Smith, and Drew (1939) on the plasma potassium content of cardiac blood at death are of interest. These authors found that in pathologic states, caused by intestinal obstruction, intestinal fistula, hemorrhage or trauma, the concentration of potassium in the cardiac blood at death in the cat averaged 42.8 mg. per cent. In four dogs poisoned with potassium this average was a little higher, 59.5 mg. per cent. The average venous plasma potassium in sixty young human adults was 17.2 mg. per cent (range 13.5 to 21.5). The average plasma potassium of human cardiac blood taken

at death was 29.8 mg. per cent. These authors concluded, therefore, that the human cardiac muscle is more susceptible to potassium than that of certain other animals. This conclusion is true, of course, only if the hyperpotassemia was the cause of death, but the authors do not state that.

More recently, Scudder, Corcoran, and Drew (1940) have extended the observations on the increase in serum potassium to cadaver blood. In twenty-seven cases the average concentration of the serum potassium was 101 mg. per cent. This high value is approximately 3.5 times the concentration found at death and nearly 6 times normal values. Experiments indicated that ammonia production might be responsible for this rapid diffusion of potassium from the cells into the serum. Furthermore, it was believed that the diffusion was accelerated by the fact that the cadavers were not placed immediately in a refrigerator. The writer spent two days in Yondine's laboratory and learned the type of case that Yondine used for obtaining cadaver blood. Only one of Scudder and his co-workers' twenty-seven cases would strictly come under this head; namely, a case of multiple fractures of the skull with a serum potassium of 72. Since this reading is elevated, although not as markedly as the average of the others, Scudder's point is not much weakened. Drew, Edsall, and Scudder (1939) have recently reported that, while there is little loss of red cells over a period of thirty days in heparinized blood, the plasma potassium content increases tenfold.

De Gowin, Harris, and Plass (1940) found that during blood storage, the potassium of the erythrocytes diffused into the plasma where it attained a maximum concentration in two weeks. Transfusion into human beings of blood with maximum plasma potassium was accompanied by no clinical, chemical, or electrocardiographic evidence of toxicity. It is to be remembered, however, before applying this dictum too literally that there is enough potassium in 3 liters of blood to cause death. Therefore, avoid transfusion of preserved blood in large amounts.

Zwemer and Scudder (1937) produced shock in cats by extensive crushing of tissue, intestinal manipulation, acute pancreatitis, intestinal obstruction, and hemorrhage. These animals developed blood potassium levels similar to those found in animals with severe adrenal insufficiency or shocked by intraperitoneal injections of potassium salts. Rises of 50 to 100 per cent were not uncommon and high potassium levels were also found in the fluids obtained from closed body cavities. These authors concluded on the basis of the findings:

"Since the effect of excess potassium in extracellular body fluids is in many respects similar to that of histamine, and as injections of histamine are followed by increased blood potassium (Thaler), our

findings are not inconsistent with those of Cannon, who holds that shock is due to a histamine-like substance."

In direct opposition to Sendder and associates (1937) with regard to the rise of plasma potassium following high intestinal obstruction is the paper of Greenwood, Haist, and Taylor (1940), of Toronto. These authors found that the plasma potassium fell in all of their animals from 17 to 40 per cent of the initial values during the first few days after operation. A post-mortem rise occurred in some cases, but was considered to be of little probable importance. These authors concluded that "in dogs changes in plasma potassium do not play an important part in causing death following acute intestinal obstruction."

Brewer, Larson, and Schroeder (1939) have also studied plasma potassium. These authors found that a single injection of 1 c.c. of 1:1,000 adrenalin would give a transient rise in potassium content from

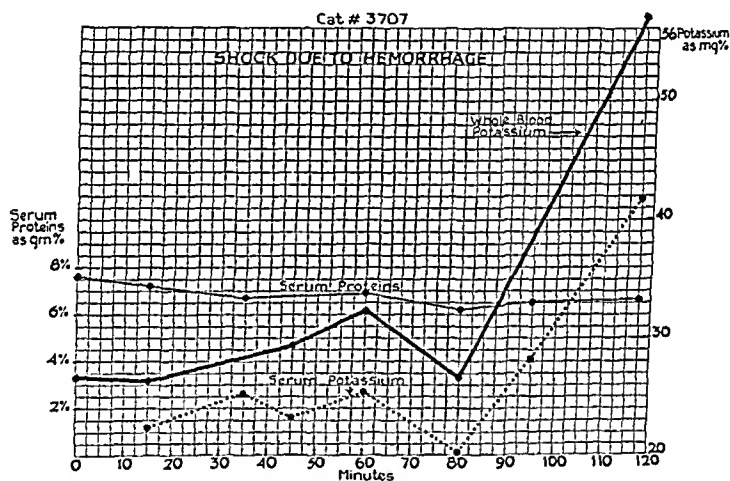


Fig. 3.—Blood potassium increase in experimental shock due to hemorrhage. (From Zwemer, R. L., and Scudder, J.; SURGERY 4: 515, 1938.)

a normal of 17 to 18 mg. per cent to a level of 19 to 22 mg. per cent. The rise was more marked in arterial than venous blood and was followed by a fall to below the previous normal level. This effect was observed in both dogs and man. Swingle and colleagues (1938) found no significant change in the serum potassium accompanying fatal adrenalin shock in normal or adrenalectomized dogs. They even said: "It is obvious that adrenalin shock has no relation to serum electrolyte changes. . . . In none of the experiments on either intact or adrenalectomized dogs were we able to correlate the shock symptoms and circulatory collapse (from adrenalin injections) with either hemoconcentration or serum electrolyte changes."

Zwemer and Scudder (1938) found the blood potassium to be increased in experimental shock. On the other hand, Bisgard, McIntyre, and Osherhoff (1938) found that in traumatic shock there was "no

consistent alteration of sodium, potassium, or chlorides." These latter authors also found no consistent change in high intestinal obstruction. This is consistent with the results of Jorgensen, Dietz, and Hill (1940), who concluded that "hyperpotassemia cannot be considered as a contributing factor to the cause of collapse and death in experimental intestinal obstruction in the dog."

The review of Scudder, Drew, Corcoran, and Bull (1939) of their studies on blood preservation includes observations later presented in Scudder's book. Important conclusions include:

1. Potassium transfer from cells to plasma begins as soon as blood is withdrawn. At the end of ten days 25 per cent may have left the cells, and at the end of thirty days 50 per cent. The rate is influenced by the following factors: (a) Shaking increases the transfer. (b) The size of the plasma cell interface in a bottle where the cells have settled is of great importance. The authors suggested tubes rather than wide flasks, and later (1940) advised hourglass-shaped bottles.

2. Potassium diffusion occurs independently of hemolysis.

The observations summarized in Scudder's book (1940) are of especial importance in considering the importance of hyperpotassemia in shock. Scudder observed twenty-eight cases of shock, twenty-six of which showed changes in the plasma potassium. A 100 per cent mortality occurred in those having an increase of over 100 per cent in the plasma potassium value. In contrast there were no deaths in the group showing an increase up to 25 per cent. A 71 per cent survival rate occurred in the cases with increases up to 50 per cent; whereas, in those whose plasma potassium had increased between 50 and 100 per cent, only 38 per cent lived. Concurrent sepsis tended to make the values low, even when the condition was serious.

Experimentally, Scudder found in 28 cats that hemoconcentration and hyperpotassemia often occurred. That the former preceded the latter casts some doubt on the probability that the latter is an *initiating* factor in shock. Further discussion of Scudder's work is included in the section of the present review devoted to his book.

Many previous workers studied potassium changes. Sunderman (1931) studied a series of pneumonia patients and found that the potassium concentration in the serum was increased in over one-half the patients. Atehley, Richards, and Benedict (1931) studied blood electrolyte changes during histamine shock in dogs. An increase in total serum base invariably occurred, but, in the only case where the potassium was determined separately, it showed no significant change. An excellent review of the potassium changes in shock was made by Eppinger (1938), of Vienna.

In the dogs in the series of Swingle and his co-workers (1938) the serum potassium did not increase in the animals subjected to intestinal

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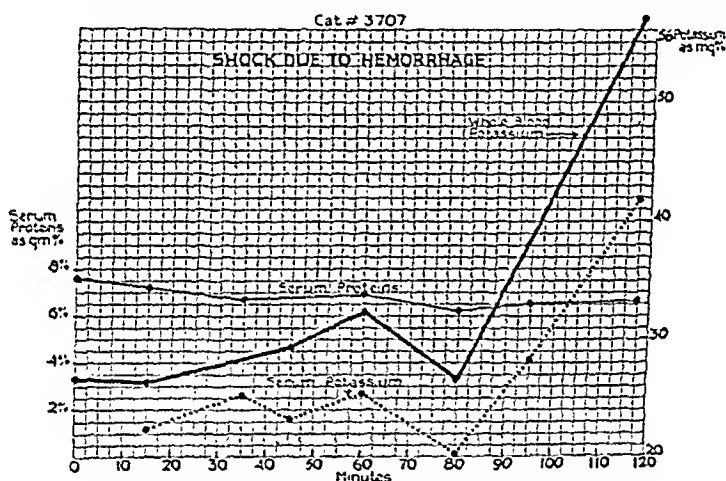


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after hemorrhage serves to protect the vital centers against the harmful effects of a dangerously low blood pressure." This action protects the vital centers but causes decreased blood flow in the remainder of the body. This gives stasis and increased capillary permeability, and the resultant loss of fluid renders the shock worse. Thus, an essentially protective mechanism results in a vicious circle. The peripheral tissues are not so important qualitatively, but quantitatively their action in fluid loss is of importance. In the sympathectomized dog this preferential treatment was found to be lost, and minor hemorrhages did not result in such a marked blood pressure fall. The sympathectomized dogs were not able, however, to tolerate as extensive hemorrhages as the normal dogs. In all these experiments the peripheral blood flow seemed to be a more accurate prognostic index than the blood pressure. Freeman (1933, 1939) also showed that prolonged activity of the sympathetic nervous system, whether resulting from the injection of adrenalin or from the spontaneous activity of the pseudoeffective state, resulted in a decrease in the circulating blood volume. This decrease could be prevented by complete sympathectomy.

That the adrenal medulla is overactive in shock is substantiated by the presence of an elevated blood sugar, as shown to be the case in postoperative shock by Gale (1935) and others. Bedford (1917) recognized the increased activity of the adrenals in shock, stating: "Increased quantities of epinephrine are thrown into the blood during conditions of low blood pressure and shock." The studies of Doménech-Alsina (1933), indicating the decreased sensibility to adrenalin in certain shock states, fit in well with the idea that the animal organism itself has an increased production of adrenalin during shock. Doménech-Alsina (1937) in experiments on dogs concluded that the maintenance of arterial pressure after hemorrhage does not have a direct relation to the production of adrenalin. This is somewhat in opposition to the results of several workers, including Bedford (1917) and Tournade and Chabrol (1925). Schlossberg and Sawyer (1933) found that sympathectomized rats were more sensitive to hemorrhage than normal rats.

Davis (1937) compared shock produced by repeated hemorrhage, trauma to the extremities, and injections of adrenalin or histamine. He found that in adrenalin shock the tissue changes do not resemble those produced by hemorrhage or trauma. The lungs are much more edematous and the heart is always dilated. The liver frequently shows areas of vacuolization of the hepatic cells with areas of central necrosis which are not found in shock resulting from trauma or hemorrhage. Other differences are that in adrenalin shock the thyroid gland shows a vacuolization and some disappearance of the colloid in the acini and a mild hypertrophy of the living epithelium. In histamine shock there

stripping, and the general tendency was for this electrolyte to decrease when the animal was in collapse. Only two of the six dogs subjected to muscle trauma showed a significant potassium increase. This increase seemed to be more dependent on the time interval since the trauma than on the severity of the circulating failure and shock. It should be remembered that these experiments involved the use of adrenalectomized rather than normal dogs. Recently Fenn, Wilde, Boak, and Koenemann (1939), of the University of Rochester, have shown that partial or intermittent occlusion of the arterial blood supply of a muscle results in an increase in the potassium content of the venous plasma. Excessive slowing or complete stagnation did not seem to increase further the amount of potassium. Stewart and Rourke (1938) reported a lowering of serum potassium associated with operation and ether anesthesia in human beings. In none of these patients, however, was the blood loss more than 13 per cent of the blood volume. Myers and Muntwyler (1940) have recently reviewed the significance of potassium changes in the blood. Suddler (1940) advised gastric lavage to wash out the high potassium containing gastric secretion present in shock. Lucena, Peregrino, Ramos, and Bethlem (1940) noted an increase in blood potassium and decrease in the sodium following surgical operation. Larson (1940) has demonstrated that epinephrine injections depress the serum potassium level in cats. This would make the potassium elevation theory of shock hard to fit in with the syndrome of epinephrine shock. Stiekney (1940) found no relation between the potassium balance in resting muscle and adrenalin injections. Zwemer and Truszkowski (1936) discussed the relationship between the adrenals and potassium.

3. ROLE OF THE ADRENAL MEDULLA. VASOCONSTRICTION IN SHOCK.—The historical development of the concept that the vasomotor center is intact and the peripheral vessels constricted in all but terminal shock has already been traced. The role of overaction of the adrenal medulla, as a factor not only in producing this condition, but actually in partly causing the shock itself, has recently been re-emphasized, especially by Freeman (1933, 1935). Freeman and also Tomb (1937) have even suggested the possibility of ergotoxine in the treatment of shock to counteract this overaction of the sympathetics. Early views on this subject of adrenalin include those of Henderson, Prince, and Haggard (1917): "We conclude that prolonged excessive secretion of epinephrin (if it occurs under pain) is not a critically important factor in the production of shock. It is therefore improbable that surgical shock is a result of excessive secretion of the suprarenals secondary to sensory stimulation."

Freeman's hypothesis is that the vasoconstriction associated with shock is not only an accompanying but also a causative factor. Freeman, Shaffer, Scheeter, and Holling (1938) stated: "Vasoconstriction

value, but the intestinal flow was still 20 per cent below its original state.

The recently developed "digital plethysmograph" by Johnson (1940), of St. Luke's Hospital, Chicago, may furnish new information on clinical shock problems. This instrument records graphically the pulse waves in a finger. While other types of peripheral and central circulatory conditions have been studied, so far it has not been applied to shock cases. This instrument does not record the absolute pressure, merely relative pressures and volume changes in the form of a pulse wave.

Observations upon *capillary pressure* have been made by Szántó (1937), of Budapest. This author observed the capillary pressure determined according to the method of Herzog in a series of operative cases. Readings were taken preoperatively and at varying intervals after operation. Minor operations caused little change, but operations where shock occurred were followed by a fall in capillary pressure. Before operation the capillary pressure averaged 40 to 50 mm. Hg. After severe operations there was a fall of 10 to 15 mm. Szántó concluded: "Decreased capillary pressure may be regarded as a component part of surgical shock." It is to be noted that these decreases were not markedly greater in relative amount than the fall in arterial blood pressure which somewhat limits their specific value as a prognostic or diagnostic sign in shock.

In summary it would seem that the presence of adrenal medullary overaction with (secondary) overaction of the sympathetic nervous system and peripheral vasoconstriction definitely is a factor in shock. It certainly begins early in the course of shock, but whether it is an initiating, accompanying, or perpetuating factor is difficult to determine. Furthermore, if it is merely a symptom, so to speak, whether its treatment is of benefit per se or whether it is a protective mechanism and should be left alone has not been completely decided. For some years the author has made the empirical observation that this overaction of the adrenals may occur most markedly in young persons. If such a young person is submitted to an operative procedure accompanied by considerable loss of blood, he will show a much more marked primary elevation of blood pressure than older persons. It would seem as though the adrenals were either very easily stimulated or the pliable vessels of young persons especially easily constricted.

4. ROLE OF THE ADRENAL CORTEX. HORMONE REGULATION OF CAPILLARY PERMEABILITY.—The function of the adrenal cortex is intimately tied up with that of the adrenal medulla and with the regulation of the sodium-potassium balance in the body. Early work on the significance of the adrenal cortex chiefly centered around the similarity between shock following adrenalectomy and other types of shock. Latterly, attention

are evidences of extreme vascular congestion in the splanchnic and thoracic viscera. Davis concluded: "The tissue changes present in adrenalin shock differ from those of hemorrhage and trauma, and this does not lend support to the concept of an excessive adrenal activity playing the major role in secondary shock."

Hamlin and Gregersen (1939) obtained results at variance with those of Freeman (1933). These authors used unanesthetized cats and found that in both normal and sympathetomized animals adrenalin caused an increase in plasma volume. Normal cats anesthetized with nembutal do show a reduction in plasma volume, but this is so slight as not to cause the volume to fall below the preanesthetic level. It would be of interest at this point to compare dosages, for different workers used different amounts of adrenalin.

Freeman (1939) 0.008 mg. adrenalin per kilogram per minute for 90 min.	Swingle et al. (1938) 0.010 to 0.015 mg. adrenalin per kilogram per minute for 60 min.
Hamlin and Gregersen (1939) 0.35 mg. adrenalin per kilogram per minute for 24 min.	

These doses are considerably larger than those used by Prohaska, Harns, and Dragstedt (1937) for their chronic hypertension experiments where no shock resulted (namely 0.0009 to 0.003 mg. per kilogram per minute). It would seem that several factors would have to be considered besides the dosage; first, the duration of the injection, and second, whether the injection kept the blood pressure elevated, indicating decreased peripheral blood flow.

Other work has been recently reported having a bearing on this aspect of the shock question. Penner and Bernheim (1939) recently surveyed the post-mortem records of the Mount Sinai Hospital, New York City, for the last ten years and found forty cases of acute post-operative and diphtheritic enterocolitis. These followed a number of conditions, but "the one finding that was present in all the cases was shock." They postulated that the shock gave decreased blood flow and vasoconstriction in the intestines with resultant anoxemia of the wall and finally transudation of plasma and even necrosis. The work of Rein and Rössler (1929) tends to support this view which explains the engorgement of intestinal villi, etc., occurring in shock as well as does Moon's toxemia theory. In one of Rein and Rössler's experiments a blood loss equaling 2 per cent body weight resulted in a 20 per cent drop in blood pressure in eight minutes. Simultaneously the flow through the intestine decreased 70 per cent and through the femoral artery 82 per cent. Ten minutes after cessation of the bleeding the blood pressure was only 5 per cent below its control value and the femoral artery flow had actually risen to 30 per cent above the initial

(1933) presented a table (see Table VII) showing that of thirty-two different factors, all but two were similar to shock and hemorrhage, and one of these was not definite.

The one discrepancy, as they pointed out, is that in adrenal insufficiency the blood sugar is low, while in traumatic shock it is normal or elevated. Freeman (1933) took this as a point of departure to disagree with Swingle and associates and while agreeing with them that a type of shock certainly follows adrenalectomy, this does not mean that adrenal insufficiency is the cause of all shock any more than, since insulin shock resembles ordinary shock in many particulars (and it is to be noted also gives a low blood sugar), therefore, all shock is due to hyperinsulinism.

Swingle and co-workers (1938) performed other experiments on the reaction of adrenalectomized dogs. These dogs developed fatal shock when submitted to various traumatizing procedures (i.e., intraperitoneal glucose injection); whereas, animals primed with hormone reacted like dogs with normal adrenals. The adrenalectomized dogs exhibiting circulatory collapse promptly reacted to intravenous injections of hypertonic saline solution with restoration of blood pressure and hemoconcentration to normal. The effect was temporary and the fluid was not held in circulation unless cortical hormone was given. The writers attributed the cause of death from adrenal insufficiency to "capillary atony, with resulting dilatation, stasis, and peripheral vascular stagnation and believe that the cortical hormone is concerned with the maintenance of capillary tone and therefore regulatory control of the volume capacity of the circulatory system."

Swingle and co-workers (1937) extended their work to show that losses of water and electrolytes to the exterior of the body by way of the urine are not *necessary* accompaniments of adrenal insufficiency in dogs.

Swingle and co-workers (1938) have recently modified their earlier views (1935) to a contrary opinion in certain regards. They more recently held that in shock in adrenalectomized animals the hemoconcentration, when present, and loss of effective circulatory fluid volume are due to factors other than sodium or chloride and associated fluid changes. In their experiments the levels of serum sodium and chloride remained unchanged, even when the animal became moribund and it was evident that the circulatory collapse was not due to disturbance of the extracellular electrolyte pattern with resulting upset in the internal distribution of body water between extracellular (including vascular) and intracellular compartments.

In these experiments strong vigorous dogs who had been bilaterally adrenalectomized some months previously and kept on maintenance doses of adrenal cortical hormone were used. Seven were subjected

was paid to the treatment, both therapeutic and prophylactic, of shock states with adrenal cortical hormone, both synthetic and natural.

*Shock Following Adrenalectomy.*—It has been known for some time that bilateral adrenalectomy will cause shock and death. Early studies of the Princeton group, including Swingle, Pfiffner, Parkins, Vars, Bott, Donahue, Taylor, and Hays (1933-1937), have shown that such shock is quite similar to surgical and traumatic shock and that, furthermore, adrenalectomized dogs are more susceptible to various agents commonly known to produce shock (intestinal stripping, hemorrhage, trauma, etc.). Those authors also showed that the various physiologic and chemical changes accompanying such shock due to adrenalectomy could be largely prevented or, if present, relieved by adequate adrenal cortical hormone dosage. In fact the similarity to shock was so striking that Swingle, Pfiffner, Vars, Bott, and Parkins

TABLE VII

CONDITIONS EXISTING IN ADRENAL INSUFFICIENCY (ANIMALS) AND TRAUMATIC SHOCK (MAN)

(From Swingle, Pfiffner, Vars, Bott, and Parkins (1933))

1. Blood volume	Decreased
2. Blood pressure	Decreased
3. Hemoglobin	Increased
4. Hematocrit	Increased
5. Red cell count	Increased
6. Venous pressure	Decreased
7. Rate blood flow	Decreased
8. Blood viscosity	Increased
9. Hemoconcentration	Increased
10. Cardiac output	Decreased
11. Venous return to right heart	Decreased
12. Heart rate	Increased
13. Heart condition	Normal apparently
14. Weak, fast pulse	Present
15. Vasoconstriction	Present
16. Ability to dilute	Lacking
17. Blood nonprotein nitrogen and urea	Increased
18. Alkali reserve	Decreased
19. Basal metabolism	Decreased
20. Blood sugar	Decreased in adrenal insufficiency Normal or slightly above in traumatic shock
21. Body temperature	Decreased
22. Use vasoconstrictor drugs	Ineffective
23. Effect forcing fluids	Beneficial
24. Vasomotor center	Normal apparently
25. Sensitivity to painful stimuli	Decreased
26. Sensitivity to cold	Increased
27. Sensitivity to anesthetics	Increased
28. Sensitivity to histamine	Increased in adrenal insufficiency, ac- tion unknown in shock
29. Sensitivity to infections and toxins	Increased
30. Urine volume	Decreased
31. Sensitivity to hemorrhage	Increased
32. Sensitivity to trauma and operations	Increased

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In these experiments strong vigorous dogs who had been bilaterally adrenalectomized some months previously and kept on maintenance doses of adrenal cortical hormone were used. Seven were subjected

to intestinal stripping and six to muscle trauma. In most instances the amount of trauma was not such as to produce shock in normal animals. Hemococentration to a rather marked degree occurred in some instances but not in others. It was apparent, therefore, that in the type of animal employed in these experiments hemococentration is not a necessary accompaniment of shock. In those cases where it does occur, fluid was lost both locally and generally. These writers stated in this regard: "We do not attribute the increased permeability of the capillaries directly to lack of cortical hormone; rather, we assume, that it is due to the general capillary atony, dilatation and stasis which results from lack of hormone."

Adrenal cortical hormone exerted a very striking effect in reviving the animals in the experiments by Swingle and associates and in restoring the blood pressure. Hypertonic saline solution given intravenously when profound shock existed raised the arterial pressure to normal levels. In the absence of cortical hormone, however, the effect was temporary and the animals soon lapsed into a shock state. The significance of these experiments is yet to be finally determined.

Swingle and co-workers (1938) performed intestinal manipulation experiments on adrenalectomized dogs that led them to conclude that the cortical hormone exerts a direct effect upon blood pressure which is distinct and separable from the action of the hormone upon blood volume and fluid and electrolyte distribution. When the dogs were in collapse following the manipulative procedure, an intravenous injection of 3 c.c. per kilogram body weight of hormone was given, followed by gradual but steady improvement in the blood pressure. Since the serum electrolytes (Na, K, Cl) showed little change in these experiments, and, since about one-half of the dogs did not show hemococentration or loss of extracellular fluids when in profound shock, the hormonal action seemed to have a somewhat specific blood pressure raising function. Other observations include those of Britton and Silvette (1933), who reviewed the theories of corticoadrenal function. The especial importance of urinary chloride determinations in Addison's disease has been stressed by Butler, Power, and Wilder (1938). Weil and Browne (1939) reported an increased excretion of cortin in the urine after surgical operations.

*Therapy of Shock With Cortical Hormone.*—Early observations on the value of adrenal cortical extract include those of Marmorston-Gottesman and Perla (1931). These authors found that adequate cortin injections could bring the resistance to histamine of suprarenalectomized rats almost to normal. Reed (1938) studied the use of adrenal cortical extract in obstetric shock. .

The results of Heuer and Andrus (1934) furnish additional evidence for the efficacy of adrenal cortical extract in at least certain types of

shock. These authors found that the intravenous injection of aqueous extracts of fatal high intestinal obstruction loops caused a primary and secondary fall in blood pressure. The latter was associated with a loss of plasmalike fluid from the circulating blood. Immediate injection of adrenal cortical extract had a marked effect both in prolonging the life of the animal and in preventing the drop in blood pressure and lessening the amount of plasma loss. Once shock had been present for an hour or more, however, neither intravenous saline solution, blood, etc., or adrenal cortical extract alone was of much avail. A combination of these treatments, on the other hand, had a markedly beneficial effect.

One of the most recent reviews of the use of adrenal cortical preparations in the treatment of Addison's disease is that of Ferrebee, Ragan, Atchley, and Loeb (1939). These authors used the synthetic compound desoxycorticosterone acetate or propionate (synthesized by Reichstein in 1935) and found very drastic effects. Over a ten-day period the following determinations showed a marked rise: serum sodium, body weight, serum volume, total blood volume, interstitial fluid volume, and systolic blood pressure. The following determinations showed a corresponding significant decrease: serum potassium, serum sugar, serum nonprotein nitrogen, serum protein, and serum cholesterol. Ragan, Ferrebee, and Fish (1939) studied the effect of desoxycorticosterone acetate upon plasma volume in patients during ether anesthesia and surgical operations. They found that the fall in plasma volume that occurred in control cases is not present when patients have been given desoxycorticosterone acetate subcutaneously three to four hours before operation. Perla (1939) reported that an excess of sodium chloride will markedly increase the resistance of rats to large amounts of histamine. Perla, Freiman, Sandberg, and Greenberg (1940) reported that desoxycorticosterone acetate and cortin combined with saline solution will prevent histamine shock in rats and mice and operative shock in human beings. The eleven patients upon whom the clinical conclusions were based might not have developed shock without the treatment, but at least did very well with it. A recent editorial (1940) in the *Journal of the American Medical Association* commenting on this article warned against too early enthusiasm.

Varangot (1940) favored the use of desoxycorticosterone in the prevention of shock. Selye and Dosne (1940) showed that desoxycorticosterone overdosage in the rat leads to hypochloremia and adrenal atrophy. Selye and Bassett (1940) have also recently shown that synthetic adrenal cortical extract (desoxycorticosterone) causes marked diuresis accompanied by increased chloride retention.

Selye and Dosne (1940) pointed out that, while pure corticosterone seems useful in the treatment of shock, even if all the slaughter house

to intestinal stripping and six to muscle trauma. In most instances the amount of trauma was not such as to produce shock in normal animals. Hemoconcentration to a rather marked degree occurred in some instances but not in others. It was apparent, therefore, that in the type of animal employed in these experiments hemoconcentration is not a necessary accompaniment of shock. In those cases where it does occur, fluid was lost both locally and generally. These writers stated in this regard: "We do not attribute the increased permeability of the capillaries directly to lack of cortical hormone; rather, we assume, that it is due to the general capillary atony, dilatation and stasis which results from lack of hormone."

Adrenal cortical hormone exerted a very striking effect in reviving the animals in the experiments by Swingle and associates and in restoring the blood pressure. Hypertonic saline solution given intravenously when profound shock existed raised the arterial pressure to normal levels. In the absence of cortical hormone, however, the effect was temporary and the animals soon lapsed into a shock state. The significance of these experiments is yet to be finally determined.

Swingle and co-workers (1938) performed intestinal manipulation experiments on adrenalectomized dogs that led them to conclude that the cortical hormone exerts a direct effect upon blood pressure which is distinct and separable from the action of the hormone upon blood volume and fluid and electrolyte distribution. When the dogs were in collapse following the manipulative procedure, an intravenous injection of 3 c.c. per kilogram body weight of hormone was given, followed by gradual but steady improvement in the blood pressure. Since the serum electrolytes (Na, K, Cl) showed little change in these experiments, and, since about one-half of the dogs did not show hemoconcentration or loss of extracellular fluids when in profound shock, the hormonal action seemed to have a somewhat specific blood pressure raising function. Other observations include those of Britton and Silvette (1933), who reviewed the theories of corticoadrenal function. The especial importance of urinary chloride determinations in Addison's disease has been stressed by Bantler, Power, and Wilder (1938). Weil and Browne (1939) reported an increased excretion of cortin in the urine after surgical operations.

*Therapy of Shock With Cortical Hormone.*—Early observations on the value of adrenal cortical extract include those of Marmorston-Gottesman and Perla (1931). These authors found that adequate cortin injections could bring the resistance to histamine of suprarenalectomized rats almost to normal. Reed (1938) studied the use of adrenal cortical extract in obstetric shock.

The results of Heuer and Andrus (1934) furnish additional evidence for the efficacy of adrenal cortical extract in at least certain types of

control group had a mortality of 62 per cent and survived an average of only 8 hours. These experiments indicated the relative inadequacy of desoxycorticosterone as compared with adrenal cortical extract, but this conclusion is rendered less definite by the introduction of a second variable into the experiments; namely, the absence of postoperative injections in some of them (*vide supra*).

Scudder (1940) also used cortical extract with salt solution clinically in twenty-seven cases. These included instances of postoperative shock, burns, hemorrhage, sepsis, intestinal obstruction, perforated duodenal ulcer, and acute pancreatitis. In general the results were good. A coincident hypopotassemia seemed to afford somewhat of a contraindication to the use of adrenal cortical extract.

*The present status of the use of adrenal cortical hormone in the treatment of shock* is hard to describe. The remedy seems to offer much promise, but the full extent of its usefulness and contraindications is not yet defined. Many of the clinical reports contain short lists of operations treated with cortical hormone without the development of shock that in my experience would not have developed shock even without cortical hormone if reasonable plasma balance had been maintained. There may be dangers in the use of cortical hormone, and Scudder (1940) has stated that in septic shock cortical extract may be harmful.

5. TOXINS, HISTAMINE, AND TISSUE METABOLITES.—The toxic theory of shock was chiefly promulgated by Quénu (1918) in France and by the Shock Committee in England at the same time (Cannon and associates). Since this work was done shortly after the early work of Dale (1910) on histamine, this drug was the chief suspect. It is of interest in this connection to note that Sir Henry Dale recently stated: "With regard to the possible role of histamine, we know now, what we did not know then, that of all the major tissues of the body, the muscles contain least of that substance. Whatever else it may have been, the shock following the Bayliss-Cannon limb trauma was not histamine poisoning." The two questions now to be discussed are: (1) Is a toxin active in shock? (2) If so, is it histamine?

*Histamine*.—Of all the toxins imputed as being the cause of shock, histamine heads the list. There are probably two reasons for this fact: first, that histamine was one of the first autogenous vasodepressants to be studied considerably; and second, that the time of this study only shortly antedated World War I, when shock was also the center of attention. One of the earliest studies was that of Dale and Laidlaw (1910), who investigated the blood pressure depressing effects of histamine ( $\beta$ -iminazolyethylamine). This substance was found in depressor extracts of intestinal mucosa by Barger and Dale (1911). Further studies soon followed and in 1919 Dale and Laidlaw reported studies showing that, along with the fall in blood pressure

material in North and South America could be secured, it would be insufficient to make such compounds available on a large scale. Thus, it took 400 pounds of cattle adrenal to make 50 mg. of pure corticosterone. Some hope is held out for obtaining sufficient quantities of corticosterone from the urine of domestic animals. The inefficacy of desoxycorticosterone seemed to indicate that the hydroxyl group on carbon atom 11 is important for the shock-combating action of adrenal steroids. Furthermore, the inefficacy of adrenal cortical extract mixtures is due to the presence of impurities which counterbalance the beneficial effects of the pure corticosterone.

Selye (1937) showed that the adrenal cortex hypertrophies following the exposure of an animal to a damaging agent. Weil and Browne (1939 and 1940) reported that cortin is excreted in the urine of patients under conditions of damage. In another article (1939) these authors stated that there is an increased excretion of cortin following surgical operations, reaching a maximum between the second and fifth postoperative days, and then gradually falling to the preoperative level. These experiments indicate an increased function of the adrenal cortex as a response to general organism injury.

Selye, Dosne, Bassett, and Whittaker (1940) studied experimentally the relation of the adrenals, thymus, and shock. They pointed out that mild trauma produces adrenal hypertrophy and thymus atrophy, the so-called "countershock phenomena." The countershock is caused, they believe, by increased adrenal cortical secretion. Preoperative administration of the latter would seem unwise, as it caused atrophy of the adrenals. These writers then went on to point out that desoxycorticosterone has proved inactive in their experiments on shock, while most cortical extracts were so crude as to be likewise inactive. They found that a reasonably pure cortin was effective in ameliorating shock in white rats produced by intestinal trauma or subcutaneous formaldehyde injection. Repeated small doses were necessary. They concluded as follows: "In the case of continued treatment with high doses of desoxycorticosterone the substance proved not only inactive but actually harmful."

At the same time as the article by Selye and co-workers (1940), Weil, Rose, and Browne (1940), also reporting from McGill University, offered further evidence for the value of adrenal cortical hormones in the treatment of experimental shock. Ether-anesthetized rabbits were given shock by means of trauma to the intestines. One group received cortin and desoxycorticosterone acetate, both preoperatively and postoperatively; the second group received preoperative desoxycorticosterone only, while the third control group received no medication. The first group had a mortality of 19 per cent and survived an average of 15 hours; the second group had a mortality of 46 per cent and survived an average of 14.6 hours, while the third

In further experiments he used Barsoum and Gaddum's (1935) extraction method, which eliminates substances other than those of histamine-like character acting on the isolated guinea pig intestine. Minard's investigations revealed that blood returning from a traumatized extremity of a dog contains a distinctly greater amount of histamine-like substances than venous blood from the opposite normal extremity, the increase averaging 80 per cent in six experiments. No appreciable change was observed in the histamine equivalent of arterial blood and venous blood from normal extremities before trauma and after the animal was in profound shock. Minard was unable to state as a result of these investigations whether this local increase after trauma was or was not significant. Macdonald and Woolfe (1938), of Manchester, compared the histamine equivalents of the blood from normal and traumatized limbs in a series of cats, usually shortly before the death of the animal. The increase in this series was markedly less than that found by Minard (1937) and not even constantly present. These authors concluded that the slight rise might be due to ischemia of the tissues, and that there is little justification for assuming that histamine is liberated in significant amounts from damaged tissues in acute traumatic shock. Code and Macdonald (1937) also reviewed the histamine-like activity of the blood.

One of the most important blows to the histamine theory of shock comes from the paper of Dragstedt and Mead (1937). These authors showed that, while experimental shock could not be duplicated by intravenous histamine injections, subcutaneous and intramuscular injections would reproduce it in many respects. Testing the blood and thoracic duct lymph of these dogs for histamine gave positive results while similar dogs suffering from traumatic (trauma to intestines or extremities) shock gave negative analyses. They conclude:

1. "We failed to find any vasodepressor 'toxin' in the blood and lymph of dogs during experimental surgical shock."

2. "Experiments indicate that if the vasodepression of surgical shock was due to a toxemia such as that of histamine, the methods employed would have been adequate to detect it."

Phemister and Handy (1927) found no evidence of histamine in traumatized blood. Simonart (1928), Blalock (1930), and Herbst (1934) also found no toxin. Schneider (1930) found no evidence of toxins when he injected blood from traumatized patients into animals. Carlton (1935) opposed the toxemia theory and O'Shaughnessy and Slome (1935) stated: "Our first conclusion is that a toxemia due to the elaboration of histamine, or any other depressor substance manufactured in the traumatized area, plays no part in the syndrome of traumatic shock."

accompanying experimental histamine shock, there was a hemoconcentration, in some cases quite considerable (hemoglobin rise to 148 from a control of 96, and hematocrit rise to 50 from a control of 33). These authors attributed the hemoconcentration to an increased permeability of the peripheral vessels with outflowing of blood plasma. Atchley, Richards, and Benedict (1931) confirmed these findings in experimental histamine shock.

Shortly after Loewi and Dale focused attention on acetylcholine and other autogenous depressor extracts, in the early 1930's a new wave of interest involved the role of these substances in shock. Chang and Gaddum (1933) studied the mechanism of extraction of the substances affording new impetus by the advantages of their new chemical technique with trichloroacetic acid extracts. Acetylcholine in particular was studied by Dudley (1933) and the work of Euler and Gaddum and others of Dale's associates at the National Institute for Medical Research (Hampstead) gave new information on acetylcholine, adenosine, H-substance, and other vasodepressants. The contributions of workers at the Institute are of great importance in the understanding of vasodepressor substances. This work, for which Dale received the Nobel Prize, includes the observations of Euler and Gaddum (1931) on the P substance, Dale and Gaddum (1930), Dale and Dudley (1931), Dale and Feldberg (1934), Feldberg and Gaddum (1934), and the comprehensive review of Dale (1934). The results of this work showed that histamine is only one of the many depressor substances.

There are still many advocates of the toxic theory of shock. Hooker (1920) was one of its supporters. Its popularity at the close of World War I is indicated by the following quotation from Krogh's monograph (1922) in which he referred to the Special Investigation Committee on Surgical Shock (1919): "The work of the Committee has proved conclusively that traumatic shock is due primarily to the action of toxic substances formed in the injured tissue."

König (1934), in Germany, believed that intermediary products of nuclear disintegration cause shock and collapse. Lurje (1936), in Moscow, advocated the toxic theory, finding a great increase in the amino acid nitrogen following operation. Aird and Henderson (1937) further showed that the histamine content of the peritoneal transudate from strangulated cat intestine increases until, after twenty-four hours of strangulation, it reaches a maximum of 1:5,000 to 1:20,000. The total content may amount to 4 mg., but they do not believe this is the sole lethal factor present.

The recent work of Minard (1937) has advanced the study of blood histamine. This author showed that in certain species, e.g., the rabbit, a large proportion of the blood histamine is in the platelet fraction.

acetylcholine in lowering the blood pressure. Doménech-Alsina (1933) studied histamine hypotension. His researches indicated that loss of fluid at the level of the digestive tract is of probable predominant importance in the production of hemoconcentration in dogs following histamine administration.

The work of Lewis and his associates also tended to favor the importance of a histamine-like substance. The studies of Lewis and Harner (1927) on the evidence for release of such a substance from injured skin, of Harris (1927) and other papers from the University College Medical School helped to advance this idea. More recently, the research of Barsoum, Gaddum, and Smirk (1935, 1936) at the University of Cairo has put forth new evidence for the histamine hypothesis. These authors have developed a new technique for determination of blood histamine, supposedly capable of detecting 0.02  $\gamma$  per cubic centimeter of blood. They found more in the corpuscles than in plasma and found an increase after release of a constrictor to an extremity and after burns. The relation of the increase in burns to the presence of shock in that condition was so variable, however, that they stated: "The relation of this rise in blood histamine to secondary shock is uncertain. There was no clear evidence of any correlation between the blood histamine and the clinical condition of the patient." This is especially true since the blood histamine did not reach its maximum until an average of ten days after the burn, long after shock usually occurs.

The important work of Menkin (1936-1940) on inflammatory exudates has considerable bearing on the histamine hypothesis of shock. Exudates from burns and other types of human or experimental inflammatory processes were injected intracutaneously on a rabbit's abdomen. Simultaneous injection of trypan blue into the ear vein caused a marked collection of the dye around the abdominal wheal, indicating increased capillary permeability in that area. The active factor is nonprotein, nitrogenous, dialyzable, and precipitated by concentrated ammonium sulfate. It seemed, according to Menkin, to be an intermediary breakdown product of protein metabolism, probably belonging to the group of relatively simple polypeptides. It had no similarity to histamine. In a later paper (1939) he calls it "leukotoxine." This substance has both a permeability factor and a chemotactic factor. It does not contain histamine or resemble histamine as far as contractile effect on an isolated strip of guinea pig intestine. The studies of Cressman and Rigdon (1939) on capillary permeability and inflammation and the influences of narcosis on the degree of permeability are of interest in connection with Menkin's work. The recent work of Hughes (1939), of St. Mary's Hospital, London, on the capillary permeability-increasing factor of various inflammatory exudates is also of interest in this regard.

It is to be remembered that Moon advocated a toxic theory and showed pictures of tissues from histamine and traumatic shock both engorged while hemorrhagic shock gave dry organs. O'Shaughnessy and Slome (1935) reported findings quite contradictory to those of Moon. They stated: "The postmortem appearances in animals whose death has followed the administration of histamine differs [sic] significantly from those seen after death from traumatic shock." They then described the typical picture of histamine shock with its capillary congestion, congested viscera, etc., and continued: "In striking contrast to this, the characteristic feature after death from traumatic shock is a general pallor of the viscera, especially of the intestines, and of the omentum." Other data on Moon's theory are discussed in the section on his book.

However, histamine shock is not entirely dissimilar to traumatic or hemorrhagic shock, as shown by the experiments of Butler, Beard, and Blalock (1931). These authors determined the blood volume, plasma volume, red blood cell count, hemoglobin, and chloride content of blood before and after a low blood pressure had been produced by the subcutaneous injection of histamine, by the removal of blood plasma, and by the removal of whole blood. The injection of histamine produced alterations that were similar to those which accompanied the removal of blood plasma. Furthermore, histamine led to a decrease in the water content of striated muscle similar to that produced by trauma, by burns, and by the removal of blood plasma.

The experiments of Wilson and Roome (1936) are of importance with regard to the toxic theory of shock. These authors found that centrifugated extracts of traumatized limbs obtained by means of a hydraulic press caused no blood pressure fall when perfused in a second heparinized animal; indeed, a slight pressor effect was obtained. Similar extracts of traumatized muscle alone were slightly toxic but did not produce a sustained fall in blood pressure or death. Roome and Wilson concluded that: "The findings do not support the 'toxic theory' of the etiology of traumatic shock." Fender and Guptill (1936) interpreted their experiments as arguing against the presence of a toxic factor in traumatic shock. In two experiments a normal dog was connected to a traumatized dog for a period of two hours by blood vessel anastomosis and then separated. The normal dog recovered. These latter experiments are all right as far as they go, but they are too incomplete to prove anything.

*Tissue Metabolites.*—In this country general knowledge of the choline vasodepressor compounds has been especially advanced by Hunt and Renshaw (1930-1936) of Harvard University. Their studies are especially interesting in that they show that these substances are so often found occurring naturally in the body. It is of historical interest that Hunt and Taveau (1906) were the first to show the dramatic effect of

and Dragstedt (1940) have shown that trypsin will liberate histamine from tissues.

The possibility, therefore, is yet to be ruled out that tissue metabolites, not exactly toxins and not histamine, are active in shock. If so, they may be of importance in causing a generalized loss of fluid from the blood stream. On the other hand, even though present, they may be only secondary to some other process as anoxia.

6. NERVOUS FACTORS.—The nervous theory of origin of shock might be said to have been the leading theory up to the time of World War I, when Cannon, Quénu, and others introduced the traumatic toxemia theory. Both Meltzer's theory of inhibition and Crile's theory of exhaustion are variants of the nervous theory. At present it seems that the original nervous injury is seldom great enough to be an initiating factor in shock. Some, such as Mahaffey (1938) and Rehn (1937), still support the nervous theory. Rehn (1937) in his monograph entitled *Der Shock und verwandte Zustände des autonomen Systems* ascribes to just what he says in his title; that is, the nervous theory of origin. This work is largely based on "theoretical-clinical" reasoning.

Simonart (1928) concluded, as a result of experiments on cats, that an intact nerve supply is essential for the production of traumatic shock, but he has since modified this view. Blalock and Bradburn (1930) found the shock that results from central nervous system trauma to differ in important respects from the following hemorrhage. The role of the hypothalamus in the regulation of blood pressure has recently been reviewed by Leiter and Grinker (1934).

The paper of O'Shaughnessy and Slome (1935) introduced new evidence in favor of the nervous theory of shock and especially influenced London and Continental thought. One hundred cats anesthetized by chloralose (0.08 Gm. per kilogram body weight) were used in their experiments, which can be divided into the following groups.

A. *Experiments to Determine the Presence of a Possible Toxin.*—

1. *Occlusion of Venous Return:* O'Shaughnessy and Slome showed that ligation of the femoral vein (as practiced by Parsons and Phemister, 1930) or of the common iliac vein (as practiced by Holt and Maedonald, 1934) is insufficient to prevent completely the venous return from a limb. Effective occlusion was attained by ligature of the femoral vein and its tributaries in the groin and the external, internal, and common iliac veins, and the inferior vena cava and its transverse ilio-lumbar tributary. However, a limb, when so isolated, still produced lethal shock when traumatized.

2. *Perfusion of a Traumatized Limb:* This likewise gave no evidence of a toxin.

3. *Vivisection:* This type of experiment also gave no evidence of a toxin.

In line with the work of Menkin, Rigdon (1940) has shown that intradermal adrenalin inhibits the localization of trypan blue in areas of inflammation produced by xylol application. This xylol reaction (Rigdon, 1940) can be accentuated by a substance obtained from certain tissues of normal rabbits. The recent report of Lambert and Rosenthal (1940) on liberation of a histamine-like substance on stimulation of sympathetic nerves may lead to possible bridging of the gap between the "histamine" and "sympathetic overactivity" theories of shock. The further studies of Minard and Rosenthal (1940) on the use of thymoxyethyldiethylamine in counteracting certain histamine actions in dogs may be of therapeutic import.

Rose and Weil (1939) found that, during anaphylactic shock in the rabbit, a marked decrease in total blood histamine occurred, and that no increase in plasma histamine was observed. In a series of clinical cases with varying degrees of shock, as manifested by clinical signs, hemoconcentration and blood pressure fell and the blood histamine level was low, as compared with control values and those after recovery. The total blood histamine was also low in agonal states, and in shock cases the decrease was greater in the more severe instances. Rose and Browne in a second paper (1940) pointed out that this decrease may be due to localization of the histamine in the injured tissues or the gastrointestinal tract. Therefore, the absence of an increase in the blood does not necessarily mean that histamine is not an active factor in shock production.

The possible relationship between the histamine and the adrenal theories of shock might possibly be explained by the recent reports of Karady, Rose, and Browne (1940) working at the Royal Victoria Hospital, Montreal. Adrenalectomy produced a diminution in the histaminase content of the lungs of rats maintained on a standard diet and given normal saline solution to drink. If water were substituted for the normal saline solution, an even greater diminution occurred. Finally the diminution of histaminase in the lung tissue of the adrenalectomized rat could be restored to within normal limits by the administration of adequate amounts of cortin.

Feldberg and Kellaway (1938) and Feldberg, Holden, and Kellaway (1938) have made important studies on histamine liberation and action. They showed that "cobra venom contains a lecithinase which splits off oleic acid from lecithin. The resulting rest, lysocithin, is powerfully hemolytic." This substance can be tested for by injection into the anterior chamber of a rabbit's eye. The recent studies of Katz (1940), demonstrating that the sensitized rabbit cells will liberate histamine *in vitro* when placed in contact with antigen, have possibilities in the study not only of anaphylactic shock, but also of the histamine hypothesis of shock in general. Ramirez de Arellano, Lawton,

The work of Shumacker, Lamont, and Metcalf (1939) on cross circulation of normal animals indicates the complexity of factors that may arise in shock cross-circulation experiments. Their studies show how poorly worked out are the control shifts of blood and fluid. Until the range of these factors is established, this type of experiment cannot be properly applied to the more complex question of shock. Or, in other words, if we don't know what happens when two normal dogs are cross circulated, how are we to appraise what happens when one of them is traumatized? Bell, Clark, and Cuthbertson (1938) did cross-circulation experiments, applying trauma to the transfused hindlimb of a recipient cat. A marked fall in blood pressure of the donor occurred, followed by death, while the recipient was practically unaffected. These results are the opposite of those of O'Shaughnessy and Slome (1935).

The experiments of Blalock and Cressman (1939) indicated that the type of anesthetic agent alone may have been an influencing factor in O'Shaughnessy and Slome's results. In the English experiments chloralose was used to anesthetize cats. Blalock and Cressman used both dogs and cats and both nembutal and chloralose in similar experiments. In none of the nembutal experiments was there evidence of the importance of nervous impulses in the genesis of shock. In cross-circulation experiments in which trauma was applied to a transfused hindlimb of the recipient animal no positive evidence as to the deleterious effects of nervous impulses was obtained, confirming the findings of Bell, Clark, and Cuthbertson (1938). The only positive evidence at all as to the importance of nerve impulses was obtained in the series of cats anesthetized by chloralose in which preliminary and repeated spinal anesthesia apparently exerted beneficial effects. This was not found in cats anesthetized by nembutal or in dogs anesthetized by either nembutal or chloralose. In these experiments local loss of fluid seemed to be the chief, even if not the only, factor.

The recent article of Lorber, Kabat, and Welte (1940) again swings the pendulum towards emphasis on the nervous factor in traumatic shock. These authors stated that their experiments were designed to test the reality of a nervous factor in traumatic shock and shed no light on the relative importance of this as compared with other causative factors. They found that shock could be produced in the perfused limb of the cat separated completely from the general circulation and communicating with the body only by means of its nerves. While this result agreed with that of O'Shaughnessy and Slome (1935), unlike these British authors, Lorber and associates found that deep anesthesia favored rather than hindered the development of shock.

The recent report of Freedman and Kabat (1940) tends to confirm that of Lorber, Kabat, and Welte (1940) that the nervous factor is

O'Shaughnessy and Slome concluded from these experiments that toxins do not play a marked role in traumatic shock. They then continued with:

*B. Experiments to Determine the Extent of Fluid Loss by.—*

1. *Bisection Experiments:* In twelve cats the excess weight on the traumatized side averaged only 32 per cent of the calculated blood volume. Since some cats developed shock with only 20 per cent fluid loss, they argued that there must be some additional factor.

*C. Experiments to Test the Importance of the Nervous Factor.—*

1. Shock will occur even if the arteries to a traumatized limb are ligated. Previous workers had argued from the lack of shock after artery ligation that fluid loss is the dominant factor in shock. Because of lack of knee jerks in such a preparation, O'Shaughnessy and Slome refer to it as an "anemic limb" and postulate that the accompanying possible anesthesia may explain the lack of development of shock. If such a limb is perfused with the blood of a second cat, the first cat will develop shock after trauma. This shock is accompanied by a decreased bleeding volume and is apt to be fatal. This experiment is used to favor the nervous theory. Aside from its complexity, its chief objection is that the donor cat died before the traumatized animal.

2. *Nerve Blockage Experiments:* Blockage of nervous impulses by (1) nerve section, (2) spinal cord section, (3) spinal cord destruction, and (4) spinal anesthesia indicated that these procedures helped to prevent shock.

O'Shaughnessy and Slome concluded from these studies: "A toxemia due to elaboration of histamine or any other depressor substance manufactured in the traumatized area, plays no part in the syndrome of traumatic shock. We regard the two remaining factors, local fluid loss and the discharge of nociceptive nervous stimuli, as the effective etiological agents. The evidence does not allow us to dogmatize as to the relative importance of these factors, although we are inclined to believe that the nervous factor dominates the picture."

Three years later, Slome and O'Shaughnessy (1938) extended these experiments, and in addition, made records of nerve action potentials, showing them to be markedly exaggerated in the afferent nerves coming from a traumatized limb, even though the trauma had been produced some time before. These latter observations of Slome and O'Shaughnessy were not confirmed by Cressman and Benz (1939), who found no consistent increased barrage of nerve impulses in the nerves of the traumatized limb in an anesthetized animal. They occasionally found increased nerve impulses in nerves of untraumatized as well as traumatized extremities. Those present in shock may be due to impulses from the tactile and proprioceptive endings. In addition, these impulses might not be nociceptive.

# Review of Recent Meetings

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## THE FIFTIETH ANNUAL MEETING OF THE WESTERN SURGICAL ASSOCIATION, DEC. 6 AND 7, 1940, TOPEKA, KAN.

JAMES S. HIBBARD, M.D., WICHITA, KAN.

THE Western Surgical Association held its fiftieth anniversary meeting on Dec. 6 and 7, 1940. The scientific sessions were held at the Topeka Municipal Auditorium and the other events were held at the Hotel Jayhawk.

Herbert H. Davis, Omaha, Neb.: **Cystic Disease of the Breast. A Critical Review.**—The author opened his paper by reviewing different etiological theories. The endocrine factor is most popular. Davis believes that it is due to an abundance of the gonadotropic factor of the pituitary at the time when the ovarian factor is on the decrease, because most cases occur between 35 and 50 years of age, at which time the ovarian hormone decreases. He does not feel that the cystic type is important as far as a tendency to develop malignancy is concerned, but that the adenocystic type is important in this respect. His cases showed a greater occurrence of carcinoma than other reports in the literature. He found cystic disease distant from the carcinoma in numerous cases of carcinoma of the breast. Also, cases of cystic disease which later developed carcinoma were cited.

John Ogilvie, Kansas City, Mo., stated that he had relieved symptoms with estrogenic substance in large quantities, but, if the breast was removed later and examined, the pathologic changes were the same as if no estrin had been given. O. J. Campbell, Minneapolis, Minn., still feels that cystic disease is not a precursor to carcinoma except possibly in a few of the adenocystic cases. He said that two more of his previously reported series of 294 cases had developed carcinoma. Now a total of 5 have developed cancer.

Paul B. Magnuson, Chicago: **Joint Débridement; Surgical Treatment of Certain Types of Arthritis.**—The author stated that early stages of arthritis should be relegated to the medical service, while complications should be considered surgical. Marked changes in the joints are caused by wear and tear and overstrain. Toxemia, infection, and metabolic processes are only contributing factors. He showed some interesting experiments on dogs which demonstrated that cartilage never heals from side to side, but that, if an area is gouged out leaving normal edges surrounding the area, no disability results. Activity is necessary to produce a degenerative type of arthritis. He showed films demonstrating severe joint injury with no arthritis in contrast to mild joint injury which allowed the patient to use the joints and ultimately to develop arthritis. He showed cases with narrow joints with spurs and irregularities which he had operated upon with excellent results. He stated that all pathologic areas must be removed, allowing fibrocartilage to fill in and leave a good joint surface. He stressed the fact that it was not necessary to do a synovectomy. Early motion was recommended.

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of considerable importance in traumatic shock. Traumatizing the hindlimbs of cats in a way to minimize fluid loss, shock still resulted. The average fluid loss in the traumatized limb was 0.85 per cent of the body weight. The means used to keep fluid loss at a minimum was to elevate the limb and keep it bandaged with three layers of adhesive tape. These authors found, in addition, that chloralose given following the trauma greatly increased the susceptibility of the animal to traumatic shock. Shock was effectively prevented in such experiments by preliminary transection of the upper lumbar spinal cord. Adrenalin produced a greater rise in blood pressure during shock than before trauma, except just before death when the response of blood pressure to adrenalin suddenly disappeared. Finally, as a result of this observation, these authors concluded: "No evidence was found to support the theory that hyperactivity of the sympathetic nervous system is responsible for the type of shock resulting primarily from afferent nerve impulses."

Volpitto, Woodbury, and Hamilton (1940) have shown that the arterial and venous pulse contours differ radically in cases of hemorrhage or traumatic shock as opposed to shock of neurogenic origin. Leveuf (1940) stated that in shock there is a relative overaction of the vagus and underaction of the sympathetic nervous system. This is, of course, contrary to practically all other published reports. The fact that Fender (1937) stimulated the splanchnic nerves of dogs for eight hours a day, six days a week, for five and one-half months without producing any lasting effect on the resting level of blood pressure might be an argument against the nervous theory of shock.

*(To be continued in the March issue. The references will accompany the last part.)*

Verne C. Hunt, Los Angeles, mentioned the large volume of pancreatic juice that drained from a pancreatic fistula in one of his cases (1,630 c.c. during twenty-four hours).

John M. McCoughan, St. Louis: **Pancreatic Fistula: Clinical and Experimental Observations.**—Six cases of pancreatic fistula were reported, 2 of which resulted from external trauma, 3 from injury at operation, and 1 from acute pancreatitis. In 1 case the fistula was transplanted to the stomach with a successful result. In 3 cases the fistula closed spontaneously. Irradiation of the pancreas by x-ray was tried in 1 case, but it did not cause the fistula to close. Observation showed that, although there was an increased flow following the intake of water, peptone, and protein, a fatty meal produced the greatest increase in secretion from the fistula. Glucose and atropine decreased the secretion, and epinephrine stimulated the flow.

Frank L. Meleney, New York City: **The Historical Aspects of Surgical Infections.**—Meleney reviewed the history of surgical infections from antiquity up to fifty years ago. The prevention of putrefaction was studied before its cause was known. The use of carbolic acid as an antiseptic was suggested by the fact that it deodorized the sewerage of certain towns in England. In 1867 Lister stated that for six years he had taught that bacteria was the cause of suppuration. In 1881 the principles of Lister were accepted in England, but in 1882 the majority of the members of the American Surgical Association were still anti-Listerian. No detailed description of hospital gangrene is to be found in Lister's publications apparently because it was so common and everyone was so familiar with it that a description was considered unnecessary. Hospital gangrene appears to have been used to describe various degrees of acute and chronic infections. Meleney thinks that bacteriology in surgery has not had the attention it should have from surgeons.

Waltman Walters, Rochester, Minn.: **Carcinoma of the Stomach.**—The author reviewed all the cases of carcinoma of the stomach seen at the Mayo Clinic since 1908. Twenty-five per cent of all cases gave an ulcer type of history. Eighty per cent had been treated previously by medical regimen for ulcer with relief. Considering those cases in which resection was carried out, 75 per cent gave positive x-ray evidence of carcinoma, 10 per cent were reported as benign ulcer, and 11 per cent were found to be operable after being reported inoperable by x-ray examination. Fifty-eight per cent of the total number were operated upon, 45 per cent were just explored, and 26 per cent of the total were resected. There was an average mortality of 16 per cent in all resected cases. Twenty-five per cent survived ten years; 15 per cent, fifteen years; and 10 per cent were living twenty years after operation. A significant finding was the fact that, when the survival curve for these patients was plotted, it was parallel after six years with the expected mortality curve for the same age, indicating that a patient who has survived six years after resection for carcinoma of the stomach rarely has a recurrence. Walters wished to emphasize that a high percentage of cases present typical ulcer histories and that only a short medical test period (three weeks) should be used.

E. Eric Larsen, Los Angeles: **230 Patients Subjected to Gastric Resection by 50 Surgeons.**—A study of the records of 230 patients from three hospitals on whom a partial gastrectomy had been done by fifty surgeons was reported. The diagnosis was carcinoma in 89, duodenal ulcer in 46, gastric ulcer in 70, and recurrent or previously operated cases, 31.\* Reichel-Polya procedure was done in 117, Balfour-Polya in 34, Hofmeister-Finsterer (post.) in 26, Hofmeister-Finsterer (ant.) in 5,

\*These figures are only approximately correct, probably due to the reviewer's error.

**Ralph G. Carothers, Cincinnati, Ohio: Treatment of Cotton's Type of Fracture of the Ankle.**—Carothers mentioned the fact that, although Cotton's type of fracture is not common, it is not unusual. He said that it is one of the most treacherous types of fractures, but good results could be expected to follow good treatment. He gave a description of the fracture and methods of reduction. The mild group with no dislocation can be reduced with down and forward traction and marked dorsal flexion. The foot is held in this position and a good skin plaster cast is applied. The group in which there is a backward dislocation of the astragalus with a more marked deformity may be treated in a like manner, but there is a tendency for a recurrence of the dislocation. The group of severe fractures with both malleoli off presents a difficult problem and, if reduction cannot be obtained by manipulation, skeletal traction should be applied through the os calcis. In about ten days a skin plaster cast may be applied. Absolutely no motion should be permitted in the cast and no walking iron should be used. They are kept in plaster eight weeks, followed by an elastic bandage.

**G. M. Morrison, Boston,** pointed out that a few cases must be openly reduced. He described in minute detail the reduction with the warning that severe cases should have no weight-bearing for ten to twelve weeks. **Ralph M. Carter, Green Bay, Wis.,** demonstrated his method of fixation which consisted of running Kirchsner wires through the bones of the foot, through the joint into the tibia to prevent slipping after application of the cast.

**William R. Cubbins, Chicago:** The Conservative Treatment of Fractures of the Shaft of the Femur.—A complete and detailed description was given of the conservative treatment used at Cook County Hospital, showing the simple Balkan frame and the low-hanging, large ring Thomas splint. Adhesive plaster traction can be used successfully but should not extend above the site of fracture. In order to prevent dermatitis due to adhesive plaster, the limb is not shaved. Cubbins showed films demonstrating the necessity of open reduction in some cases, as well as films of cases showing the misuse of plates, screws, etc.

**Ralph M. Carter, Green Bay, Wis.,** stated that he preferred skeletal traction. **Francis E. Clough, San Bernardino, Calif.,** stated that slow union should not be classed as nonunion, that heel pain meant pressure on the tendon achilles and not on the os calcis, and that cutting out the plaster over the heel aggravates the pain. The majority of cases are nonoperative. **Ralph G. Carothers, Cincinnati, Ohio,** stated that the maximum amount of weight should be used in the beginning. He said that metal plates applied in transverse fractures become loose because there is absorption of bone at the ends which produces a space between the bone ends and allows motion which loosens the screws.

**Thomas G. Orr, Kansas City, Mo.:** Resection of the Head of the Pancreas and Duodenum for Carcinoma.—The literature was reviewed, beginning with the 2 cases reported by Whipple in 1935 and including 14 cases subsequently reported. In Orr's case a cholecystectomy had previously been performed so that at the first stage the common duct instead of the gall bladder was anastomosed to the stomach and a gastroenterostomy was performed. Three weeks later a V-shaped excision of the pancreas, including the pylorus and duodenum, was performed. The patient was readmitted six weeks later, at which time a pseudocyst of the pancreas was drained and a pancreatic fistula resulted. This fistula was still persistent at the time of the report. There has been a 33.33 per cent mortality of the cases reported. Orr suggested that the use of lipocaine to prevent fatty infiltration of the liver might reduce this mortality.

very important, evidenced by a mortality of only 2 per cent when only the appendix was removed.

**Raymond W. McNealy and Manuel E. Lichtenstein** (by invitation), Chicago: **Strangulated Femoral Hernia Sac Without Abdominal Contents.**—The authors stated that the contents of a femoral hernia should be expected to become strangulated in a rather considerable number of cases, but that strangulation of the sac alone was infrequent. They reported 10 cases occurring in a series of 401 cases of femoral hernia. They discussed the anatomy of femoral hernias and explained that trauma to a femoral sac may cause inflammation with obliteration of the neck and accumulation of fluid within the sac. Thrombosis and edema then will produce strangulation. A history of trauma accompanied with pain in the groin and a tender discolored mass suggest this condition.

**Stuart H. Harrington**, Rochester, Minn.: **Diagnosis and Treatment of Substernal Types of Diaphragmatic Hernia.**—Harrington reported 4 cases of substernal hernia occurring in a series of 270 cases of various types of diaphragmatic hernia. This space, the foramen of Morgagni, was described as a weak region, and probably these hernias are not traumatic in origin, since none gave a previous history of injury. Their anterior position as shown on the x-ray film would immediately classify them as substernal, although the x-ray films might suggest tumor. Two of the cases had been previously diagnosed as tumor and not until exploration was the true condition found. An upper abdominal approach is the one of choice.

**Warren H. Cole and R. D. Weber**, Chicago: **Surgical Considerations in Constrictive Pericarditis.**—Three such cases were reported, 2 of which were operated upon. In 1 of the operated cases the results were good after a rather prolonged convalescence. The other case developed severe myocardial decompensation and died post-operatively. Diagnosis may be confused with cardiac failure and cirrhosis of the liver. First the patient complained of general weakness, dyspnea on exertion, ascites, and edema of the extremities. The electrocardiogram showed an eversion or flat T-wave. There was a high pulse pressure, circulatory delay, a blood volume above normal, and a low cardiac output. A small heart shadow with restriction on the right and left side is very significant. There is a 30 per cent mortality from operation, and, although the results are good, recovery is slow.

**Stuart Harrington**, Rochester Minnesota, in discussing Cole and Weber's paper, stated that too much emphasis on a small heart may lead to difficulty, and demonstrated cases with normal-sized hearts. Also, he thought it extremely important that 7 out of 9 cases at the Mayo Clinic presented areas of calcium deposit as seen on the x-ray film and at operation.

**Loyal Davis and John Martin**, Chicago: **The Surgical Problem of Unilateral Exophthalmos.**—Martin presented the paper, confining his remarks to those cases caused by tumors and arteriovenous aneurysms. He stated that the intracranial tumors most commonly found were meningiomas of the greater wing of the sphenoid, which at times were extremely vascular and difficult to manage. When due to meningiomas, pulsating exophthalmos is not present nor are superficial dilated veins necessarily seen. Cranial nerves most commonly involved are the third, fourth, and sixth. The x-ray findings are generally very helpful. An enlarged optic foramen is caused by glioma of the optic nerve as well as by meningioma, but there is an absence of bone erosion in the former. In the aneurysmal cases one sees the characteristic pulsating exophthalmos with a bruit, a thrill, and a dilatation of the peripheral

Billroth I in 34, Billroth II in 18, sleeve resection in 7, and total resection in 7 cases. The mortality for the series was 33 per cent. The mortality for resection in duodenal ulcer was 24 per cent. Larsen stated that the highest mortality followed operations by surgeons of inadequate experience and training. Since his study had been reported in staff meetings of the three hospitals, the mortality has decreased to 9 per cent.

**Arthur R. Metz, Chicago: Obstruction of Stomach Due to a Congenital Mucosal Cyst.**—The case reported is the only one in which two complete septa have been found. No similar case is reported in the literature. One septum was pyloric and the other midgastric. The patient was a Jewish male infant. Continuous vomiting was present and a mass could be felt. At operation, after the cyst was entered, openings were made in the stomach proximal to the upper septum and in the duodenum below the lower septum. There was no tract around the cyst. Radial incisions were made in the septa and a catheter was left in the duodenum for feeding purposes. Microscopic sections through the septa demonstrated normal mucosa. A gastrointestinal series disclosed a normal stomach and duodenum three years later.

**Erwin R. Schmidt and F. E. Mohs, Madison, Wis.: The Chemosurgical Treatment of Cancer, a Microscopically Controlled Method.**—The authors described a method of removing cancer under what they term microscopic visualization. It is made possible by using a technique for producing a fixation of tissue in situ, by the application of zinc chloride, so that when excised the base of the mass may be studied serially under the microscope. Areas that are positive are again treated with zinc chloride, removed, and studied microscopically until an entirely noncancerous layer is obtained. They reported 440 cases which were so treated and which were followed for from one to four and one-half years with 93 per cent free of recurrence at the site of the primary lesion. They point out that, regardless of the grade of malignancy, this treatment can be used.

**Vernon David, Chicago,** stated that, although chemotherapy has been used for ages and has been condemned by the medical profession, this method should be given a trial under the strictest conditions and reported on at a later date.

**James F. Percy, Los Angeles: Advanced Cancer of the Nose and the Accessory Sinuses; Treatment by Actual Caутery.**—Percy gave a description and showed pictures demonstrating his technique used in treating advanced cancer of the sinuses. Entrance into the maxillary sinus was made through a U-shaped incision over the sinus. The malignant growth was destroyed by actual cautery. He showed some cases in which it was necessary to extend through the dura into the brain tissue. For the prevention of meningitis he left a charred sponge closely adhering to the dura or brain tissue.

**Carl E. Black, Jacksonville, Ill.: Three Thousand Appendectomies.**—James F. Percy, Los Angeles, read Black's paper concerning an analysis of 3,315 appendectomies by the staff of Passavant Memorial Hospital, Jacksonville, Ill., which represented the work done in one small hospital by many surgeons. The first part of the period (1923-1931) showed a mortality of 5 per cent compared to a 4.48 per cent mortality for the second period (1931-1939). The mortality varied considerably according to the individual surgeon. Operator U. had a mortality of 6.8 per cent in 831 cases in contrast to Operator W-I's 0.7 per cent mortality in 274 cases. In seeking a reason for a higher mortality in the first period, the following were considered important: delay in diagnosis, delay in treatment, and inadequate pre- and post-operative treatment. Multiple surgery at the time of appendectomy was considered

were present, and a mass was felt in 72 per cent. Farr manipulation was done in all cases (air inflation with belly open) and it was successful in 83 per cent. Two cases were operated upon by the technique of Montgomery. In 4 cases excision was done, 3 with lateral anastomosis and the other with end-to-end anastomosis. Ileostomy was done in 3 cases followed by death. Ireland proposed a new procedure which consisted of injecting glycerin between the intussuscepiens and intussusceptum followed by gentle manipulation of the finger between the two. Two severe cases have been reduced in this manner.

Edwin M. Miller, Chicago, discussed the papers on intussusception, and stated that only when more cases are treated by the procedure described by Ireland (glycerin injection and manipulation) could its value be ascertained. In his own 58 cases 19 were extremely difficult to reduce. In 10 it was impossible to reduce the intussusception. Five of this group recovered after extensive resection (exteriorization). He advised placing patients on their abdomen until ready to close the ileostomy. Stanley J. Seeger, Milwaukee, Wis., discussed 60 cases from the Milwaukee Children's Hospital which showed a 33 per cent mortality, although there has been a decrease in late years. The decrease, he thought, was due to better pre- and postoperative treatment and the fact that all cases are now having immediate operation. George Packard, Denver, Colo., reported cases from the Denver Children's Hospital, with the remarkably low mortality of 6.6 per cent in the last five years. Considerable influence in keeping this mortality rate low was thought to be due to the use of postoperative suction.

Frank C. Mann, Rochester, Minn.: **Experimental Studies in Motor Mechanism of the Intestine.**—Different types of exteriorized bowel loops were discussed and the importance of a loop covered by skin was emphasized. Different levels were studied. Alvarez's theory was demonstrated in that higher segments of bowel show a greater rate of activity and the rate is decreased progressively as the cecum is approached. Definitely increased motor function followed feeding and was not affected by section of the vagus. There was a definite decrease on fasting. Liquid food increased activity, but activity was more marked and lasted longer with solid foods. Peritoneal irritation (Lugol's solution as irritant) inhibited motor activity, but not after both splanchnics were severed. Motor activity was not affected by gall bladder distention. Cascara affected activity very little, but magnesium sulfate produced a marked disturbance of all activities. Ether and operative exposure caused almost a complete secession of motor activity for about four hours. Activity decreased after enemas.

Charles Puestow, Chicago, stated that he had had an opportunity to study a human bowel loop covered by skin and it had reacted the same as does that in the dog.

Maurice Kahn, Los Angeles: **Surgical Treatment of Ulcerative Colitis.**—Kahn described the pathology of this disease, citing as complications perforation, abscess and fistula, hemorrhage, stricture, and, rarely, thrombophlebitis. He said that polyposis occurred in 13 per cent, which tended toward carcinomatous degeneration. Ninety-five per cent of the cases finally showed extension to the ileum. He felt that about 25 per cent of the cases were surgical. Ileostomy should be used at times in the acute fulminating type and the results and mortality would be much better if used earlier. Cecostomy and appendicostomy were found to give poor results. In the chronic intractable type complete colectomy should be used before the previously stated complications occur. Six cases were reported. In 2 ileostomy

veins. The cause of the exophthalmos is thought to be due to a reversal of blood flow in the ophthalmic vein with stasis and hyperplasia of the orbital contents. There are no x-ray changes seen in cases of aneurysm. Treatment of tumor cases consists of a transfrontal excision which may be difficult due to vascularity. In arteriovenous aneurysms ligation of the common and external carotid arteries is the procedure of choice, although sometimes it is necessary to ligate the internal carotid intracranially, distal to the aneurysm.

Frank R. Teachenor, Kansas City, Mo., described 1 case in which he used a lateral approach to remove a meningioma and reported 3 cases of aneurysm. Alfred W. Adson, Rochester, Minn., showed 1 case in which the internal carotid was ligated intracranially and the ophthalmic artery obliterated with a silver clip, because there had been a recurrence after previous ligation of the carotid artery in the neck.

James Barrett Brown and Frank McDowell, St. Louis: **The Late Functional Results Obtained by the Free Skin Grafting of Burns.**—Brown showed by motion picture films his remarkable results in severe burns, especially on the neck. After extensive excision of scar tissue from the neck, full thickness grafts were obtained from the abdomen and in numerous cases the whole front of the neck was restored with one graft. The donor site was covered with a split graft from the thigh.

Earl Padgett, Kansas City, Mo., discussed Brown's paper, stating that he is using the calibrated skin grafts almost entirely and feels that his results are much better and that much time is saved.

Verne C. Hunt, Los Angeles: **Hemangioma of the Large Bowel.**—Hunt reported a case of hemangioma involving the entire rectosigmoid, the rectum, and the uterus treated by a two-stage (Lahey) abdominoperineal resection and hysterectomy, with excellent results. The patient's symptoms of bloody stools with an occasional massive hemorrhage and secondary anemia dated back twenty-one years. Hunt stated that 48 cases had been reported, 20 involving the colon and 28 involving the rectum. These varied from small capillary nevi to cavernous hemangioma.

Everett P. Coleman, Canton, Ill.: **Recurring Jejunal Intussusception.**—The rarity of the condition was discussed by Coleman, who estimated that jejunal intussusception occurs in about 0.9 per cent of all intussusception cases. He discussed the general symptoms and classifications of intussusception and proceeded with the history of his case, which was of six years' duration. The patient had attacks of abdominal pain, nausea, and vomiting, which became more frequent. Barium studies failed to disclose the lesion present. Transnasal duodenal suction was used in preparation for surgery. At operation a large blue mass was found beginning 10 cm. below the ligament of Treitz. It was resected and an end-to-end anastomosis was done. The intussuscepted bowel consisted of nine layers and measured 6 feet, 10 inches in length.

Jay Ireland, Chicago: **The Treatment of Intussusception.**—The 133 cases occurring in the Children's Memorial Hospital, Chicago, from 1920 to 1940 were divided into two ten-year periods. The first period revealed a 41 per cent mortality in 5½ cases as compared to a 22 per cent mortality in the 79 cases of the second group. Ninety-one per cent were diagnosed within the first twenty-four hours, 22 per cent within the next twelve hours, 8 per cent the next twelve hours, and 27 per cent over seventy-two hours. In 92 per cent vomiting occurred. In 49 per cent bloody stools

## REVIEW OF THE SOUTHERN SURGICAL ASSOCIATION MEETING, DEC. 10, 11, 12, 1940, HOT SPRINGS, VA.

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THE annual meeting of the Southern Surgical Association was held Dec. 10, 11, and 12 at the Homestead Hotel in Hot Springs, Va. Of a total of forty listed papers, thirty-eight were presented.

1. Grover C. Penberthy, Detroit, Mich.: **Chemotherapy as an Aid in the Treatment of Osteomyelitis.**—Statistics show a lowering of the incidence of osteomyelitis in recent years, possibly the result of improved nutritional status in the underprivileged class. The present report is based on nineteen cases, with treatment and conclusions as follows: Sulfanilamide is not effective in staphylococcal infections. Sulfapyridine, along with blood transfusions, gave encouraging results. Sulfathiazol, although not more effective, was found to be better tolerated than sulfapyridine, and for this reason is preferred. Even though high blood concentration levels were maintained, untoward results from sulfathiazol were not frequent or serious. One and one-quarter grains per pound of body weight were given over a twenty-four-hour period at four- to five-hour intervals, and the dose reduced as clinical improvement occurred. Large initial doses were not given. Recently, following saucerization in chronic osteomyelitis, cavities have been packed with sulfathiazol powder. The value of local use of the drug in compound fractures was referred to. Of the author's cases, 50 per cent had positive blood cultures, most frequently staphylococcus, but, in some instances, hemolytic streptococcus. Chemotherapy has considerably reduced the period of hospitalization, as well as the incidence of secondary or metastatic abscesses. None of the author's cases had involvement of other bones after chemotherapy was started. Deformities as well as mortality have been reduced by this form of treatment.

Discussion: Frank D. Dickson, Kansas City, Mo., cited his experience with chemotherapy in twelve cases of osteomyelitis, some of which were acute. In addition to early operation he placed sulfathiazol powder into the wounds, which were then closed. The drug was also given for twelve days by mouth. All healed, with no mortality.

2. Frank D. Dickson, Kansas City, Mo.: **The Surgical Treatment of the Arthritic Patient.**—This presentation was in the form of a moving picture accompanied by remarks by the author. The persistent deformities which constitute economic and emotional adjustment problems were discussed. Of the approximately 1,000,000 cripples in the United States, some may be relieved by surgery. Surgical intervention may be indicated for: (a) incapacitating disability and (b) removal of a focus which is propagating the disease. It was emphasized that an infected synovial membrane may act as the focus of infection. In twenty-six cases in which synovectomy was performed, twenty-two cases were definitely relieved. In rheumatoid arthritis the operation must be delayed until the quiescent stage; whereas, in hypertrophic arthritis operation can be done at any time, because there

was done, in 1 an ilco-sigmoidostomy, and in 3 total colectomies. The second stage had just recently been done in another case.

In discussion, Frank Meleney, New York City, reported good results by the use of zinc peroxide (10 per cent) in polyvinyl alcohol (2 per cent) for irrigations. Best results were obtained when fed through a cecostomy.

William J. Carson, Milwaukee, Wis.: Transplantation of Fascia Lata in Cystopexy.—A case was reported which had a complete prolapse twenty-one years following a total hysterectomy. A free graft of fascia lata was cut to fit the pubic arch, being anchored to the symphysis pubis, the descending ramus of the pubis, the ramus of the ischium, the tuberosity of the ischium, and the base of the broad ligament on each side. The results were good four and one-half years post-operatively.

of England and France to make a better showing in the present war in Europe was due to their neglect in the use of the most modern types of transportation. **J. M. T. Finney, Sr.**, Baltimore, reflected on the woeful unpreparedness of the United States at the time of its entry into the World War of 1914-1918 and was impressed by present plans for preparation. He said that had it not been for efficiency, self-denial, and consecration in the last war on the part of the medical corps personnel, soldiers would not have fared so well. **Raymond T. Sullivan**, New York City, echoed Finney's remarks and lauded the work which is being done in the education of the medical personnel. **Arthur Shipley**, Baltimore, agreed with Mixer in regard to the military importance of caring for great numbers of relatively minor casualties rather than devoting much time to the hopelessly injured cases. He cited the fact that there is at present no communication zone; everything is combat zone. The mobile hospital unit which has been tried in peacetime maneuvers, he felt, would be suitable for use close to combat zones.

**4. Irvin Abell**, Louisville, Ky.: **Medical Preparedness.**—Abell reviewed the work on military preparedness being done by the American Medical Association. He discussed the need for supplying qualified physicians to industry, and referred to the need for assuring adequate care of civilian population while at the same time supplying the personnel required for military service. The provisions of the selective service act were considered, including that desirable feature whereby deferment might be obtained to avoid interfering with the training of men for future military or civilian requirements. Medical men within the draft ages, he felt, should apply for a reserve officer's commission, as otherwise they might have to do preliminary service as an ordinary enlisted soldier. The work of the National Defense Council and the Health and Medical Committee was outlined.

**5. Alfred Blalock**, Nashville, Tenn.: **Blood and Blood Substitutes in the Treatment of Shock.**—In secondary or hematogenic shock, associated with reduced blood volume, blood and blood plasma are of great value in treatment. Salt solution infusions are unsatisfactory because not only does the salt solution leave the circulation, but blood proteins are carried out also. When plasma, blood, or serum is used in the presence of increased capillary permeability, such a marked outpouring of blood proteins does not occur. For blood transfusion the vacuum bottle method was considered superior, because of its simplicity and because contamination can easily be avoided. In discussing the use of plasma, Blalock said that, although hemoconcentration is usually present in shock, the bad effects of hemoconcentration have been overestimated, especially if blood volume is maintained. A given quantity of plasma causes a greater increase in osmotic pressure than does an equal quantity of whole blood. Plasma can be stored more easily than can whole blood and the danger of reaction is less, especially if the plasma is pooled in order to decrease the concentration of agglutinins. Methods for the preparation of clear dilute plasma and dried plasma were described. Some workers prefer dried serum, while others believe that liquid plasma and dried serum are equally good. The preferences of various armies in respect to blood or blood elements were cited; i.e., the Russian army uses whole blood, the German army uses whole blood from universal donors only, the British army prefers liquid plasma.

**Discussion:** **Roy D. McClure**, Detroit, discussed a method for concentrating blood or plasma. It was found that, when blood is placed within a cellophane container, the volume of the blood is decreased, and it occurred to Hartmann that this method could be used for concentration of plasma. By this method, dry plasma can be rapidly produced. It is possible to produce dried plasma in four

is no acute phase. In addition to the moving picture illustrating synovectomy, other surgical procedures, i.e., manipulation, capsulotomy, arthroplasty, and arthrodesis, were illustrated and discussed. The use of a vitallium cap in hip arthroplasty was referred to.

**Discussion:** Charles S. Venable, San Antonio, Tex., elaborated on the use of vitallium caps in arthroplasty. He described a cap which has been devised for the head of the radius, and another employed in knee arthroplasty. Paul B. Magnuson, Chicago, discussed the effect of repeated trauma, caused by arthritic excrecences, in the full evolution and maintenance of both destructive or rheumatoid arthritis, and hypertrophic arthritis. He has done joint débridement in 62 cases, removing rough and thickened tissues. All cartilage is removed down to bare and bleeding bone. Any ridges caused by removal of cartilage should be parallel to the direction of motion. The results in his cases have been astonishing.

3. **Lieut.-Col. William C. Munly, Washington, D. C.:** Notes on Medical Service in the Present Mobilization.—The manifold medical problems involved in present-day mobilization, and the plans which have been made for their solution, were outlined. These problems were divided into two main categories; i.e., (a) the provision of adequate medical service and (b) the training of enlisted men. Plans for initial as well as for expanded hospital facilities, and for medical and nursing personnel, were discussed. Appreciation was expressed for the cooperation of various societies, universities, and other bodies which are concerned in the plan. Dental, veterinary, medical administrative, sanitary corps, and medical department enlisted personnel requirements were presented. The organization and function of enlisted specialists, i.e., laboratory, dental, sanitary, x-ray, surgical, veterinary, and pharmaceutical, was reviewed. The supplying of technicians has been undertaken by the Red Cross. Males not physically qualified for military service, as well as females, may serve in a number of civilian capacities. Station hospitals, with a total bed capacity of 68,000, will provide for 5 per cent of the military population. General hospitals, with a total bed capacity of 14,000, will provide for an additional 1 per cent of the military population. Reserve depots for medical supplies have been provided. The organization and activities of the National Health and Medical Committee were outlined. The National Research Council facilities have been made available, and at present there are seven main committees actively functioning; i.e., the committees on chemotherapy, medicine, surgery, aviation medicine, transfusion, surgical specialties, and neuropsychiatry. There is also a committee on information, and many subcommittees.

**Discussion:** Charles Mixter, Boston, discussed the care of serious casualties in advanced areas. Many cases of head, chest, and abdominal injuries are detrimental to military operations and should not be operated upon at advanced hospitals. Civilian surgeons are likely to be forgetful or to overlook the importance of operating upon a greater number of minor cases instead of expending fruitless efforts and consuming an unwarranted amount of time in operating upon hopelessly wounded cases. The transportation of the injured to base hospitals by means of commercial airplanes, the use of autogiro planes, and the use of the many presently existing landing fields, golf courses, and lakes, for the landing of planes was discussed. Harvey Stone, Baltimore, also emphasized the importance of speed in returning men to active duty. Attention should be given to the great number of relatively minor injuries rather than focusing attention on the seriously wounded individuals. Stone felt that the injured men would get better attention if they were transferred 200 to 300 miles behind active battle zones. He felt that the failure

nerves. Ochsner felt that embolectomy for arterial embolism is no longer necessary, as the gangrene resulting from embolism is due to distal spasm, and this may be successfully relieved by sympathetic block. Incidental comment was made in respect to the value of sympathetic block in the treatment of thrombophlebitis and phlebothrombosis. John C. A. Gerster, New York City, advocated that, in order to avert disastrous results from secondary hemorrhage, which is likely to occur between the seventh and the tenth days following arterial injuries, a loose tourniquet be kept around the limb, proximal to the sites of infected amputation stumps.

7. Parke G. Smith, Cincinnati, Ohio: **Urologic Surgery.**—Although no reports are yet available concerning urogenital injuries which have occurred in the present European war, a consideration of the character of present warfare makes it possible to anticipate certain things which might be expected. Previous experiences and reports reveal that 65 per cent of bladder injury cases died. The mortality in kidney injuries was 20 per cent, and even 2.5 per cent of those with wounds of the external genitals died. The importance of prompt evacuation to base hospitals of bladder or urogenital casualty cases was discussed. The differences in the present and the last World War were alluded to, especially in respect to the fact that at present there are many injuries to civilians. Injuries in modern warfare are most frequently due to crushing forces rather than to penetration and resemble the injuries which are caused in automobile accidents in civil life. In discussing the management of renal injuries, it was considered that in the instance of minimal or moderate injuries conservative treatment should be employed; when actual renal parenchymal damage has been done, exploration should be done, clots removed, and the kidney sutured; in the extremely severe injuries nephrectomy must be done. Smith referred to the increased number of bladder ruptures due to distention of the bladders of occupants of air-raid shelters, where both sexes commingle. Chemotherapy has greatly improved the outlook in respect to the control of infection following urologic injuries.

8. Daniel C. Elkin, Atlanta, Ga.: **Injuries of the Chest.**—The narrow margin of safety under which thoracic viscera functions makes thoracic injuries extremely serious, and such injuries are likely to be rapidly fatal. The management of chest wounds includes the treatment of shock, the treatment of hemorrhage, and the restoration of cardiorespiratory physiology. Pleuropulmonary wounds may be open or closed. The open wounds are much more serious and should be debrided and closed. The closed wounds are less serious, and treatment should usually be conservative, except in the instance of heart wounds. Depressed rib fractures sometimes require elevation under anesthesia. Block of the intercostal nerves, for the relief of pain, may be tried for the possible benefits which this procedure may afford. The methods for managing the following complications were discussed: pneumothorax, atelectasis, prolapse of the lung, empyema, hemothorax, traumatic asphyxia, ileus, and subcutaneous as well as mediastinal emphysema. Crushing injuries of the chest due to automobile accidents were discussed, with special reference to contusion of the heart caused by impingement against the steering wheel. In the latter type of injury the sternum and ribs may not be fractured. The treatment is entirely symptomatic. Approximately 2 per cent of wounds of the chest are associated with penetrating wounds of the heart. Attention was drawn to the importance of the rise in venous pressure and the fall in arterial pressure as indicators of cardiac tamponade. Intercostal thoracotomy, with removal of part of the sternum, was considered to be probably the best approach to heart wounds. The pericardium should be loosely closed.

hours by this method; whereas, other methods require forty hours. The dried plasma is stored in the containers used for the drying process. McClure stressed the importance of keeping the dried plasma in moisture-proof containers in order to avoid gumminess of the plasma. Waltman Walters, Rochester, Minn., advocated the collection of blood from recruits and civilians in anticipation of war needs. He also discussed the advisability of indicating the blood group of each soldier on his name plate, and referred to the transportation of casualty cases by airplane. Bradley L. Coley, New York City, relayed English opinions in regard to blood transfusion; i.e., a preference on the part of some for dried serum because it keeps indefinitely and it does not become contaminated with bacteria. He reported that the British are using from four to six pints of plasma per case.

6. I. A. Bigger, Richmond, Va.: **Peripheral Vascular Injuries.**—Bigger considered it important that practice in arterial suture in an animal experimental laboratory should precede the execution of this type operation upon human beings. He discussed the effects of spontaneous shifting of tissue planes in effecting hemostasis. Operations on arteries should be avoided in the presence of infection. Many pulsating hematomas heal without operative intervention, and for this reason not all pulsating hematomas demand immediate operative exploration. When the circulation in a limb distal to a pulsating hematoma is good, operation may be delayed. Direct suture is ideal if there is no devitalized area around the site of injury, but this latter condition frequently does not exist because in modern warfare many of the injuries are produced by high explosive shells. Venous transplants have not proved successful. The local application of sulfonamide drugs in contaminated wounds was advised in order to reduce the degree of infection. Regional heparinization was advocated and it was reiterated that silk should be employed for sutures. The following methods for the prevention of gangrene following ligation of important arteries were discussed: (a) sympathetic nerve block by novocain, before and after operation in elective cases, and following operation in the emergency cases; (b) prevention and control of infection; (c) occlusion of concomitant veins at the same level or proximal to the point of arterial ligation; (d) rest of the extremity after occlusion, with the limb placed on a level at which the veins are maximally filled; (e) avoidance of pressure; (f) maintenance of temperature at normal levels, with particular precaution in respect to the application of external heat; (g) passive vascular exercise by means of the glass boot for the application of alternating positive and negative pressure to the part was considered to be contraindicated in many cases; (h) restoration of blood volume and red blood cell content by means of transfusion; (i) the administration of oxygen by inhalation; (j) the administration of nicotinic acid; (k) the administration of papaverine for whatever good effects this drug may exert.

Discussion: John W. Price, Jr., Louisville, Ky., did not share the enthusiasm in regard to the possibility of being able to suture vessels under conditions of war practice. During the war of 1914-1918, however, he did frequently have occasion to ligate arteries. He recommended ligating concomitant veins. Deryl Hart, Durham, N. C., discussed the importance of ligating arteries both proximal and distal to points of injury. Alton Ochsner, New Orleans, La., felt that, in order to obtain full benefit from sympathetic nerve block for the prevention of gangrene following arterial ligation, this procedure should be done as early as possible. Ochsner referred to the successful ligation of the common iliac artery by Mims Gage, New Orleans, for a mycotic aneurysm, the success of the procedure being considered largely due to the preliminary blocking of the lumbar sympathetic

10. Guy A. Caldwell, New Orleans, La.: **New Developments in the Treatment of Compound Fractures.**—Although methods for treating these injuries have varied within recent years, the basic principles remain the same. Advances include better methods for the treatment of shock, chemotherapy, roentgentherapy, better operating equipment, and the use of peetin-sulfathiazol jelly. Among 300 cases at the Charity Hospital in New Orleans, there were only twenty potentially infected cases. This observation was introduced to indicate how reports on chemotherapy and roentgen therapy might be misleading in respect to the value of these agents. It was advocated that bone fragments should be withdrawn into the wound when traction splints are applied in preparation for transportation of the patient. Present improved methods for treatment of shock permit earlier débridement and assure better circulation, and there are fewer serious wound infections. The treatment of shock, if possible, should be done in the operating room. Caldwell felt that tetanus toxoid immunization will replace the administration of tetanus antitoxin. He considered gas gangrene antitoxin of doubtful prophylactic value. In discussing the preparation of the patient for operation, he deprecated the employment of soap and water and advocated the use of ether and iodine. Meticulous dissection is superior to irrigation of the wound. Instillation of strong antiseptics into the wound is undesirable. The limb should be adequately immobilized during the period of preparation as well as during operation. In Spain and Finland most wounds were left open and the incidence of gas gangrene was extremely low. Joint wounds, however, should be sutured. Lacerations over subcutaneous bones should be sutured, but counterincisions should be made. Internal fixation should be employed only in carefully selected cases. Adequate immobilization with provision for access to the wound was considered superior to encasement in plaster. The use of peetin-sulfathiazol jelly has yielded very gratifying results. It not only eliminates odors, but favors healing. In order to anticipate the development of gas bacillus infection in compound fracture cases, tissue obtained in the course of débridement should be sent to the pathologic laboratory. Zinc peroxide paste may be employed to advantage in some cases. In discussing x-ray therapy for gas bacillus infection, the author did not believe that it alone is of definite value, but he thought that it might exert an inhibitory action under some circumstances.

11. Mont R. Reid and B. N. Carter, Cincinnati, Ohio: **Traumatic Surgery.**—Reid limited his comments to the treatment of fresh traumatic wounds. He felt that this type of surgery is more exacting than many types of elective surgery which are generally considered of greater magnitude. The principles of hemostasis, débridement, and rest were re-emphasized. Antiseptics were considered harmful. A good blood supply should be maintained, both in respect to amount and quality of the blood. Healthy cells have a remarkable power to combat bacteria, and healing of wounds is brought about by growth and activity of living cells. Early assay and treatment of shock are important. The author discussed in detail: (a) management of simple incised wounds, (b) delayed closure of infected wounds, (c) treatment of contaminated lacerated wounds, and (d) infected traumatic wounds. In the instance of infected traumatic wounds tendons and nerves are not sutured primarily. The wound is packed open with vaseline and plaster fixation is afforded. The author believes that a window should not be cut in a plaster cast because herniation due to edema is likely to result at the site of fenestration. If a dressing must be done, he felt that the entire cast should be removed.

Carter showed slides illustrating the types of wounds and their treatment, as discussed by Reid.

**Discussion:** **Albert O. Singleton**, Galveston, Tex., made the interesting observation that the relative incidence of gunshot and stab wounds is related to the economic status of the negroes. In good times, when firearms are possessed, gunshot wounds are more common; whereas, in poor times, stab wounds are more frequent. At present, bullet wounds are more frequent. Singleton advocated avoidance of entering the pleura when it has not been perforated, but said that it is important to enter the pleural cavity when it has already been perforated. **Deryl Hart**, Durham, N. C., discussed what was best to do in cases, seen two to four weeks after injury, in which there is an infected hematoma. In his experience he encountered difficulty in attaining satisfactory re-expansion in such cases. **I. A. Bigger**, Richmond, Va., stated that decision in regard to the proper handling of hemothorax is sometimes difficult. When the amount of blood in the pleural cavity is large, it should be aspirated, not only to relieve pressure, but also to obtain blood which may be employed for autotransfusion, if the case is seen within the first few hours following injury. When the amount of hemothorax has been large, air replacement is advisable. Bigger expressed the belief that aspiration may be employed to advantage in cases of heart wound tamponade, either as a preliminary procedure or as a definitive treatment, especially in military practice.

In closing, **Elkin** agreed that he, too, had encountered cases with infected hematomas in which it was difficult to obtain a cure. In 1,500 cases of chest wounds studied by him, there has been only 3 per cent of infection. He believes that infection would be higher if all cases were aspirated or drained. Increased intrathoracic pressure or definite infection, he believes, should be the only indication for aspiration of the pleural space. **Elkin** did not agree that aspiration should be done in cases of heart tamponade, as it is impossible to select the cases in which this will be sufficient.

**9. Vilray P. Blair**, St. Louis: **Plastic and Facial Maxillary Aspects of Military Surgery.**—The plans which were made by the Surgeon-General for the management of face and mouth injuries in the World War of 1914-1918 were reviewed. Many faciomaxillary injuries are at once fatal. In the nonfatal cases such injuries may exert a very harmful effect on the morale of the injured individual, who may cause much expense to the government in compensation claims. For the best management of faciomaxillary injuries, it is oftentimes advisable to pair a dentist with a general surgeon. The importance of proper early treatment of these individuals was emphasized in order that long periods of disability and tedious multiple operations might be averted. **Blair** warned against the removal of any detached bone and advocated its early replacement. In the instance of wounds about the mouth in which there has been loss of considerable substance, suture of the mucous membranes of the skin, as recommended by **Tuffier**, is a very good procedure. Scrubbing out of particles of black oil, and picking out with a knife of black powder, at the site of burns shortly after injuries in which these substances have been implanted into the skin will prevent subsequent tattooing.

**Discussion:** **Robert Ivy**, Philadelphia, emphasized the fact that plastic surgery has broad aspects and is not limited to facial injuries. He agreed that cooperation with the dental surgeon is necessary for the proper management of many faciomaxillary injuries. He stressed the following elements in the management of these cases, i.e., arrest of hemorrhage, establishment of a proper airway, temporary fixation of jaw fractures before an attempt is made to close the wound, provision for safe transportation, including the placing of the patient in a face-down position on a litter. Apparatus was demonstrated which has been devised for bringing the upper or lower jaw forward. Such apparatus can be improvised by using tongue blades or wire coat hangers.

body armor, and showed slides illustrating body armor which has already been devised as well as a suggested modification, or new type of body armor, designed to afford maximum protection with minimum increased weight. Of the prophylactic measures for the reduction of the serious consequences and complications of abdominal injuries, some may be instituted beforehand, while others are applicable after injury is incurred. Measures which may be employed before injury is incurred are concerned with reducing the incidence of severity of peritonitis resulting from perforation of the hollow alimentary tract viscera. In this connection the author discussed the possibility of administering sulfanilylguanidine for the purpose of accomplishing relative sterilization of the gastrointestinal contents, as well as transforming the intestinal flora by means of preliminary administration of cultures of lactobacillus. Measures which may be employed after injury is incurred are concerned with avoidance of delays in transportation, the use of motorized mobile hospital units, the application of improved methods for the treatment of peritonitis and wound infection, and the employment of new methods for the study and treatment of shock and hemorrhage. A mobile shock cart, which consisted of a compact arrangement of the apparatus and materials used in the modern study and treatment of shock and hemorrhage, was illustrated.

14. Owsley Grant, Louisville, Ky.: **The Use of Air Pyelogram in Diagnosis.**—The use of gas or air as a medium in pyelography is not new. Difficulties following the use of air have been due to disregard of the fundamental principles of the method. Air embolism can be wholly obviated. Following a description of the method, the author reviewed the contraindications, which consisted essentially of: (a) conditions under which retrograde pyelography would be inadvisable and (b) frank renal hematuria. The air method is of inestimable value in accurately and positively locating the position of small stones or fragments of large stones. There have been no untoward effects in the author's experience, and postoperative reactions have been less than when other media have been employed.

15. J. Garland Sherrill, Louisville, Ky.: **The Management of Bilateral Renal Stones.**—The author presented a historical résumé concerning stones of the urinary tract. It is frequently difficult to decide upon the best method of managing bilateral stone cases. Some writers advise operating upon the side of the least damaged kidney first, while a contrary procedure is advocated by others. Complications are more common in bilateral calculus cases. The efficiency with which the remaining kidney takes on the function of the one which has been removed was discussed. Patients who have had bilateral stones must be advised to live in a manner which minimizes any deviation from the normal.

In discussing the last two papers, Thomas S. Cullen, Baltimore, cited some personal experiences as a sufferer from stones. Henry D. Furniss, New York City, spoke favorably of air pyelography, especially when it is desired to do a pyelogram with a patient in the erect position. He believes that carbon dioxide is safer than air. Irvin Abell, Louisville, Ky., stated that so far no studies made have elucidated the formation of renal calculi, and for this reason a rational method of treatment has not yet been evolved. Abell cited that calculi are unilateral in 75 per cent of cases and bilateral in 25 per cent of cases. In bilateral cases the stones may be of equal size, or the stone on one side may be much larger than the one on the other side. He favors removing first the stone on the side showing the greatest function. When large calculi are present on both sides, it may be better to avoid any surgical intervention. Lawrence R. Wharton, Baltimore, believes that operation should be done if possible, even when large stones are present on both sides. He emphasized conservatism in respect to performing nephrectomy.

12. C. C. Coleman, Richmond, Va.: **War Wounds of the Nervous System.**—Information is not yet available in regard to the present war injuries of the nervous system. Injuries of the nervous system were classified. Improved results in the management of these injuries must depend on elimination of delays and institution of treatment and in the standardization of the methods of treatment. The serious associated injuries frequently present in modern war injuries are responsible for many of the fatalities. Prompt evacuation and transportation, even by airplane, would be helpful in reducing the morbidity and mortality associated with nervous system injuries, but it should be borne in mind that patients with open wounds of the skull do not tolerate altitudes above 5,000 feet. Delayed complete treatment at a base is better than treatment at advanced posts, unless the facilities at the latter are unusually good. The employment of suction apparatus and electrosurgical units in the débridement of brain wounds was discussed. At times, head injury cases may be operated upon to advantage as late as forty-eight hours following injury. Unsutured scalp wounds at times may be packed with vaseline. Coleman felt that no attempt at chemical disinfection by means of antiseptics should be made. In the instance of spinal cord injuries, associated abdominal injuries or urinary tract infections frequently are responsible for death. The hopelessness of many spinal cord injuries was discussed; in many such cases operation must consist entirely of removing foreign bodies and affording drainage of infected areas in the overlying soft parts. In the management of bladder paralysis, suprapubic cystotomy is the treatment of choice, especially in war practice. Peripheral nerve injuries constituted 4.5 per cent of all casualties in the past war. Many of these cases were operated upon late, and recovery of function was very incomplete in most instances. The employment of chemotherapy for the purpose of retarding or preventing infection offers encouraging possibilities, and results at present should be better than in the World War of 1914-1918. Primary nerve suture should be done whenever possible. Autogenous nerve grafts were unsuccessful in the last war in all cases the author had an opportunity to observe. The use of fibrin as a means of maintaining nerve approximation was mentioned, but Coleman felt that the use of this substance is obviously limited to those cases in which the nerve ends can easily be approximated.

Discussion: John S. McEwan, Orlando, Fla., stated that he was active in a large hospital in France during the World War of 1914-1918. Although he did many nerve sutures, he did not have an opportunity to follow them up. He considered pieces of clothing as important causes of infection, and emphasized the importance of removing these in performing débridement.

13. Ambrose H. Storek, New Orleans, La.: **Injuries of the Abdomen—Preventive and Prophylactic Aspects.**—The destructive and complicated character of abdominal wounds incurred in modern warfare, and the difficulty of quickly transporting these casualty cases, is responsible for an appallingly high mortality rate, and is forcing the consideration of abdominal injuries from the preventive and prophylactic standpoints. Fortunately, not only are there methods whereby the present number of immediately fatal injuries can be reduced, but there are also means whereby more of the less seriously injured abdominal casualty cases may be saved. Preventive measures for the reduction of the total number of injuries include education in respect to precautions that should be taken by armed forces and civilians at times when the danger of incurring abdominal injuries can be reasonably anticipated, the provision of adequate shelters for protection in case of airplane or artillery raids, armor protection for vehicles and equipment, and the adoption of some type of body armor. The author discussed various types of materials which have been employed for

body armor, and showed slides illustrating body armor which has already been devised as well as a suggested modification, or new type of body armor, designed to afford maximum protection with minimum increased weight. Of the prophylactic measures for the reduction of the serious consequences and complications of abdominal injuries, some may be instituted beforehand, while others are applicable after injury is incurred. Measures which may be employed before injury is incurred are concerned with reducing the incidence of severity of peritonitis resulting from perforation of the hollow alimentary tract viscera. In this connection the author discussed the possibility of administering sulfanilylguanidine for the purpose of accomplishing relative sterilization of the gastrointestinal contents, as well as transforming the intestinal flora by means of preliminary administration of cultures of lactobacillus. Measures which may be employed after injury is incurred are concerned with avoidance of delays in transportation, the use of motorized mobile hospital units, the application of improved methods for the treatment of peritonitis and wound infection, and the employment of new methods for the study and treatment of shock and hemorrhage. A mobile shock cart, which consisted of a compact arrangement of the apparatus and materials used in the modern study and treatment of shock and hemorrhage, was illustrated.

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16. William Perrin Nicolson, Jr., Atlanta, Ga.: Tuberculosis of the Breast.—Tuberculosis of the breast is more common than is generally supposed. Unnecessary radical operations may be averted by early recognition of this lesion. The present report is based on seven cases. The history of the surgery of tuberculosis of the breast through 1939 was reviewed. There have been 500 cases in the literature. The suggested routes or mechanisms whereby the infection becomes established are as follows: (a) via the duct, (b) through skin or nipple abrasion, (c) through the bloodstream, (d) through the lymphatics, and (e) by contiguity of tissue. There was a history of trauma in 7 per cent of the cases. Tuberculosis of the breast is more common during the childbearing age. Early diagnosis from carcinoma is difficult. Differential diagnosis must be made from carcinoma, sarcoma, benign fibroepithelial tumors, chronic cystic mastitis, gumma, plasma cell mastitis, fat necrosis, and pyogenic mastitis. The average age was 36.4 years, with a range of from 16 to 70 years. The average duration of symptoms was 13.6 weeks. The author advocated simple mastectomy as the operation of choice. Only fourteen cases of bilateral tuberculosis of the breast have been reported. The author's case occurred in a 17-year-old girl.

Discussion: John L. McGehee, Memphis, Tenn., reported five cases in addition to those which had been reported up to 1934. These five cases occurred among 932 breast cases at the John Gaston Hospital. McGehee felt that biopsy was necessary in order to confirm clinical impressions in such cases. Julian Moore, Ashville, N. C., inquired in regard to the existence of tuberculosis in other areas in the cases reported by Nicolson. Willard H. Parsons, Vicksburg, Miss., reported the case of a patient with tuberculosis of the breast from whom three years previously he had removed a kidney for tuberculosis. A simple mastectomy was done and now, eight years afterwards, there has been no recurrence. Arthur M. Shipley, Baltimore, reiterated the possibility of confusing tuberculosis of the breast with carcinoma of the breast. He felt that in only a few instances is there evidence of tuberculosis elsewhere.

17. Frank H. Lahey, Boston: Aids in Avoiding Serious Complications in Thyroidectomy.—In a series of 19,700 thyroid cases at the Lahey Clinic, there has been a mortality of 0.76 per cent. There has been an incidence of 0.3 per cent of recurrent laryngeal nerve injury in the last 5,000 cases. There have been 10 cases of tetany in the entire series, and none in the last 4,000 cases. Lahey felt that it is important that the surgeon rather than the internist should study and prepare thyroid cases before operation. He stressed the importance of recording one's impressions when the patient is first seen in regard to the number of stages of operation which probably will be needed. Unless this is done, the improvement which results from preoperative preparation may lead to the undertaking of undesirably extensive operations. The age of the patient, the gain or loss of weight, and the duration of the disease must be taken into consideration in estimating thyroid cases. The administration of 10 per cent glucose just before operation was advocated in order to reduce the number of postoperative thyroid reactions. Lahey felt that the pulse pressure is the best single indication of toxicity. An increase or widening of the pulse pressure during operation indicates an increasing toxicity and serves to indicate that operation should be stopped. The use of local anesthesia was deprecated and, although cyclopropane was considered to be the best anesthetic, the dangers associated with the use of this substance were reviewed. Lahey has personal knowledge of three cases in which ventricular fibrillation and death followed the administration of cyclopropane, and for this reason he advocated the administra-

tion of this gas at a low concentration. As a means of observing heart function during operation, a visible electrocardiogram projected onto the wall of the operating room is now being employed in his clinic. Intratracheal anesthesia was advocated for use in many cases, and the desirability of performing tracheotomy early in cases in which there is any duskeness was stressed. Variations in the course of the recurrent laryngeal nerves were described, and exposure of the nerves during operation was advocated, as a means not only of protecting the nerves, but also of safely permitting the removal of sufficient thyroid tissue, to prevent so-called recurrence or continuance of symptoms. Inadequate exposure of the gland was considered to be a frequent cause of postoperative hemorrhage. Transverse division of the strap muscles was advocated as a routine procedure. The author illustrated cases in which poor skin scars followed thyroidectomy, and he discussed means of avoiding such disfiguring scars.

18. Warren H. Cole, Chicago, Ill.: *Precautions in the Surgical Treatment of Thyrotoxicosis*.—Since neurocirculatory asthenia, tuberculosis, and endocarditis may be confused with thyrotoxicosis, these conditions must be considered in differential diagnosis. Cole believes that ambulatory preparation of the thyrotoxic patient is desirable unless cardiac decompensation exists or unless the patient is severely toxic. It is important to recognize and to treat adequately associated diseases, such as diabetes. Mortality may be favorably influenced by employing multiple-stage operations in certain cases. The following were presented as criteria for operability: (a) gain in weight, (b) lowering of resting pulse rate to 115, (c) lowering of the basal metabolic rate to 50, (d) improvement in symptoms. Local anesthesia was deprecated and the author expressed a preference for ethylene. Allowing the patient to wait for a long time in the operating room before operation is started produces a very unfavorable psychic effect. It is usually unsafe for the surgeon to change his mind during the course of operation in regard to the extent of operative procedure. Glucose solution should be administered intravenously before and after operation. Cole gives Lugol's solution for as long as three weeks postoperatively. Tracheotomy should be done immediately when stridor indicates hemorrhage or nerve injury. Postoperative oxygen therapy is effective in preventing or treating thyroid crises.

Discussion: In considering the mechanism whereby ligature of one or both superior thyroid arteries produces a good effect, George Curtis, Columbus, Ohio, believes that improvement is not due entirely to reducing the blood supply, but that at least part of the benefit from this procedure is due to interruption of nerve conduction. There is a negative calcium balance in hyperthyroidism, and for this reason Curtis some time ago began administering calcium preoperatively along with large amounts of vitamin D, and he feels that calcium therapy has prevented severe postoperative storms in his cases. Thyroidectomy arrests the negative calcium balance. Robert Dinsmore, Cleveland, Ohio, pointed out that lowering of the pulse rate is an important index of the thyrotoxic patient's improvement. In discussing the matter of the exposure of the recurrent laryngeal nerve in the course of thyroidectomy, he observed that Lahey does not expose the entire nerve. Dinsmore expressed the belief that postoperative psychoses are not due to the hyperthyroidism or the operation for hyperthyroidism. Robert Bartlett, St. Louis, gave a brief report on a fifteen-year study of goiter cases which had been under the care of himself and his associates in private practice. In the period between 1926 and 1930, the mortality was 3.1 per cent; whereas, in the period between 1931 and 1940 the mortality was 1.7 per cent. He and his associates have not done upper

pole ligations since 1931. Since 1935 there have been no deaths in crisis, and no severe reactions have been observed. **Harold Foss**, Danville, Pa., is convinced that there are various ways of obtaining equally good results in the management of hyperthyroid patients. When the mortality is high, it indicates to him that more multistage operations should be done.

In closing the discussion, **Lahey** advised against operating on borderline or doubtful cases. He felt that patients in such cases should be allowed to go away on a trip and that they be reassessed following their return. This, he felt, will eliminate unnecessary operations. A low basal metabolic rate does not indicate safety, although a high basal metabolic rate does indicate toxicity. He felt that at least some of the benefits accruing from preliminary pole ligation were due to the conditioning of the patient to operative procedure.

**20. Loyal Davis, Chicago, Ill.: Endocrine Studies in Patients With Subtotal Hypophysectomy.**—Davis observed that, although visual disturbances may be relieved by hypophysectomy, some of the patients continue to have endocrine disturbances postoperatively. He reviewed methods for maintaining or restoring the pituitary or master gland influence on the target glands; i.e., the thyroid, the adrenals, and the gonads. Hypophysectomy causes a lowering of basal metabolic rate and a rise in cholesterol. Studies conducted in conjunction with the present work also included estimation of adrenal cortex activity by the Wilder test, carbohydrate balance, gonadotropic function, and parathyroid function. These studies were carried out in 25 cases, 18 of which were hypopituitary and 7 of which were acromegalic.

**Discussion:** **Waltman Walters**, Rochester, Minn., considered such studies as Davis had made as important in furnishing data concerning the role of the pituitary and other ductless glands, and in permitting interpretation of the confusing implications of such conditions as hypoglycemia not due to adenoma of the islands of Langerhans. **Emil Novak**, Baltimore, discussed Frölich's syndrome in relation to its gynecologic aspect. Novak spoke of the unsatisfactory status of substitution therapy due to the unknown chemical nature of the pituitary product. **Ambrose H. Storck**, New Orleans, La., noted that, because estrogenic hormones inhibit the production of thyrotropic pituitary hormones, diethylstilbestrol or other estrogenic substances have been given to a small number of hyperthyroid patients who could not be brought into good condition by means of rest, calcium, iodine, a high caloric diet, and vitamins. The number of cases in which apparently beneficial effects following this type of therapy have been observed is still small, but the results so far have been at least encouraging.

**21. J. Barrett Brown, St. Louis, Mo.: Reconstruction of Cleft Lips.**—This presentation consisted principally of motion pictures accompanied by comments by the author. Brown emphasized the importance of always letting some member of the family see a cleft lip patient before operation is undertaken. In discussing the influence of heredity in the development of cleft lip, it was observed that children of parents who have had cleft lip do not necessarily have cleft lip. Nasal correction should always be done in conjunction with the lip repair.

**Discussion:** **H. L. D. Kirkham**, Houston, Tex., pointed out that standard procedure in the repair of cleft lip is oftentimes impossible because of the many different problems which may be present in individual cases. In the instance of double defects Kirkham repairs one defect at a time. If a tight upper lip follows a repair, he transplants a piece of the lower lip into the upper lip.

22. **Howard M. Clute, Boston, Mass.: Jejunostomy for Postoperative Feeding.**—Jejunostomy for postoperative feeding was presented as a procedure which may be lifesaving. Reference was made to the relative malnutrition which is common in the general population. In stomach cases malnutrition is particularly likely to be pronounced. It is important to realize that subclinical manifestations or states of subnutrition exist, and may be responsible for postoperative hypoproteinemia. Complementary jejunostomy, performed at the time of principal operation, has been employed by the author in over fifteen cases in which there were lesions of the stomach and biliary tract. There were no deaths in this series of cases. A mixture of skimmed milk, thiamin, egg, vitamin C, and haliver oil with viosterol is administered through the tube postoperatively in amounts from 1,500 to 2,000 c.c. daily. Jejunostomy is usually performed in a loop of bowel 20 to 30 cm. below the ligament of Treitz. The first purse-string suture surrounding the jejunostomy tube is anchored to the tube, and a second purse-string suture anchors omentum to the area of the ostomy. When no omentum is present, the ostomy site is brought to the peritoneum of the wound edge. The ostomy openings have closed within from two to three days following removal of the tube, and there has not been a complicating factor in any case.

Discussion: **Shelton Horsley, Richmond, Va.,** stated that he has employed the method described by Clute, but that he prefers a mushroom catheter to a whistle-tip catheter. He subsequently cuts off the tube and allows the mushroom tip to be passed per rectum. Horsley referred to the undesirable effect produced by indwelling gastroduodenal catheters, and for this reason he does gastrostomy in many gastric resection cases. He uses a sharp hemostat instead of a scalpel for making the opening into the stomach, because this procedure produces a gridiron effect and prevents leakage when the tube is removed.

23. **Harold L. Foss, Danville, Pa., Secondary Operations on the Gall Bladder and Biliary Ducts.**—After commenting on the frequency of biliary tract disease, Foss presented observations based on 2,485 biliary tract patients in whom 140 secondary operations were performed. The average age of the patient at the time of the first operation was 40 years, and the average age at the time of the second operation was 48 years. Ninety-five of the secondary operations followed cholecystostomy, the secondary operation in most cases consisting of cholecystectomy. Thirty-three patients upon whom secondary operation was performed had had cholecystectomy and 11 of these had had a common duet stone. Six of the secondary operations revealed biliary duct stenosis. There were stones in the gall bladder or ducts in 58 per cent of the secondarily operated cases. Fifteen per cent of the cases had dilated ducts. Eleven of the cases had been operated upon two or more times before Foss saw them. In 7 of the 140 patients upon whom secondary operations were performed, nothing but exploration was done. The hospital mortality on the entire series of 140 cases was 8.5 per cent. Routine exploration of the dilated common duet was advocated. It was not considered that x-ray examination of the ducts in the operating room is practical. Foss observed that it is surprising how often the findings at the second operation are not in keeping with the symptoms and signs presented preoperatively. Cholecystectomy performed for noncalculous gall bladder disease is frequently followed by unsatisfactory results. The use of cotton for ligature and suture material was lauded and was advocated as a means of reducing the frequency of postoperative hernia and wound infection. (N.B. This paper was discussed in conjunction with the papers of Newell and Edwards, to follow.)

25. A. P. Jones, Roanoke, Va.: **A Method of Handling the Appendical Stump.**—The author reviewed the methods of treating the appendical stump which have been advocated. The blind sac produced by ligation of the base of the appendix and invagination of the stump by means of purse-string suture may become the site of an abscess which may subsequently rupture into the peritoneal cavity. Inversion of the appendix without its ligation was considered to be dangerous on account of the possibility of peritoneal contamination. It was not considered that simple ligation of the appendix is a satisfactory procedure. The author described the method which he employs, which consists of turning back a cuff of peritoneum in the region of the base of the appendix, placing a double loop of catgut about the appendix, holding the loops of catgut close to the appendix by means of hemostat, introducing a purse-string suture, and then cutting the loops of catgut close to the point where they are grasped by hemostats, and inverting the stump by means of the hemostats still attached to the remaining short loops surrounding the base of the appendix. He has employed this method in 126 cases with no mortality. Fifty of the cases had acute appendicitis.

Discussion: Shelton Horsley, Richmond, Va., contended that the simple ligation method is quick, simple, and adequate. In 1,142 cases in which this method has been employed, there have been 8 deaths, or a mortality of 0.7 per cent.

26. E. Dunbar Newell, Chattanooga, Tenn.: **Report of a Case of Rupture of the Common Duct.**—Spontaneous rupture of the common bile duct is very rare and few examples of this lesion, in which there was not associated trauma, operation, or an impacted stone, have been reported in the literature. The author was able to find only two other similar cases reported. The patient on whom the present report is based was a diabetic who had had epigastric distress for eight years. There was no jaundice. A preoperative diagnosis of ruptured peptic ulcer was made. At operation, exploration revealed a dilated common duct and there was effusion of bile under the peritoneum overlying the bile duct. Several small cholesterol stones and some "mud" were found in the duct. The gall bladder was removed and the common bile duct was drained for twelve days postoperatively. A follow-up one year later revealed the patient to be in excellent condition, having gained fifteen pounds. It was believed that the rupture occurred at an inflamed weak spot or that it might have been due to an impacted stone in the wall. Some details of the two other cases reported in the literature were presented.

27. C. R. Edwards, Baltimore, Md.: **Acute Cholecystitis With Perforation Into the Free Abdominal Cavity.**—The present report is based on twenty-one cases of acute cholecystitis which were admitted to two hospitals in Baltimore. There was an 11 per cent incidence of perforation. Only 75 per cent of the acute cases were operated upon, the rest of the perforations being found at autopsy. The history and physical signs were typical in all cases. The author does not believe that x-ray examination is important in the diagnosis of this condition. Partial resection or cholecystostomy was done in most of the cases upon whom operation was performed, but the author believes that cholecystectomy should be done if possible.

Discussion: Thomas S. Cullen, Baltimore, discussed Edwards' paper and presented observations in regard to rupture of the gall bladder, especially in respect to stones which became encapsulated after extrusion into the peritoneal cavity. Charles Gordon Heyd, New York City, in discussing Foss' paper referred to his own observations based on a review of 4,000 cases with biliary tract disease. Forty-two of the

cases required exploration of the common duct at the second operation (thirty-six of these patients had their first operation elsewhere), and in the majority of these cases calculi were found in the duct. Heyd expressed his strong conviction that cases of acute cholecystitis should be operated upon, as in most instances the rupture is associated with acute peritonitis and in only a comparatively few cases does local abscess formation occur. Before operating for acute cholecystitis, six to twenty-four hours of preparation should usually be allowed because in a group of cases operated upon immediately there was a 24 per cent mortality; whereas, the mortality is much less when preliminary preparation is done. Robert L. Rhodes, Augusta, Ga., considered that blood chemistry studies, which reveal low chloride or high uric acid levels, indicate the need for preoperative preparation in biliary tract cases. The liver should be given preeminent consideration. General hygienic care is important and will oftentimes relieve the distressing symptoms which persist in some instances following biliary tract operations. Howard Clute, Boston, in discussing Foss' paper, described a vitallium tube which has been devised for use in reconstruction operations on the common duct. Clute reported a recent successful bile duct operation on a patient who had been previously operated upon four times. George Bunch, Columbia, S. C., reported two cases in which there was an acute exacerbation of gall bladder disease during the course of treatment for fracture of the femur. In one of these cases the gall bladder ruptured, in the other case the gall bladder was found to be full of stones, but there had been no rupture of the gall bladder wall. Frank Lahey, Boston, briefly reviewed two cases in which a rubber tube was used to span defects or loss of substance of bile ducts. One of these cases was operated upon four years ago, while the other was operated upon two years ago. At present, both are well. Lahey cautioned against allowing a tube introduced into the common duct to extend into the duodenum. The tube should be of a size larger than the sphincter of Oddi. Exploration of the common bile duct is especially indicated in the presence of acute cholecystitis, in which there is frequently infected bile and stones in the duct.

**28. Warfield M. Firor, Baltimore: The Use of Sulfanilylguanidine in Surgical Patients.**—Observations and experiences based on 12 surgical patients who received sulfanilylguanidine before operation on the colon were presented. Although the author did not feel justified in formulating definite or final conclusions at present, it was considered that at least 2 of the cases would have died if the concentration of coliform bacteria had not been reduced before operation. The author also felt that the intestinal wounds in 3 cases would have failed to heal per primum without the drug. In 2 cases open anastomosis was successfully performed without the slightest evidence of subsequent infection. Firor referred to the observation of Marshall and his co-workers that this drug, when given orally, is less toxic than sulfapyridine or sulphathyzol. Sulfanilylguanidine is poorly absorbed from the intestinal tract, and the concentration of coliform bacteria in the feces of mice is greatly reduced after the oral administration of the drug. Furthermore, these workers found that the new compound is as active as sulfapyridine against pneumococcus infection in mice, and on the basis of in vitro studies they showed that it is as effective as is sulfanilamide against several other pathogenic bacteria.

**Discussion:** Leo Brady, Baltimore, stated that, through the courtesy of Firor, he and his associates have had the opportunity of using sulfanilylguanidine in 2 cases, in both of which it was considered that the administration of the drug prevented the development of peritonitis. Brady commented on the absence of nausea and vomiting, and found that the patients were willing to take the drug almost as soon as they reacted from the anesthetic. Harvey B. Stone, Baltimore, has employed

this drug in 6 cases, in all of which there was infection of the colon of one kind or another. All of the cases survived operation. He felt, however, that much additional experimental work must be done in order to evaluate fully the drug. The solubility of the drug in water, the lessened absorbability from the alimentary tract, and the specificity for the colon group obviously make sulfanilylguanidine an agent almost ideally designed for attack upon the bacterial flora of the large bowel. Apparently, the high degree of effectiveness is attained at the end of six or seven days of administration. Several days after the drug is discontinued, bacteria rapidly reappear. Therefore, it seems wise to give it for six or seven days prior to the planned operation and to continue the administration of the drug six or seven days after operation. Arthur M. Shipley, Baltimore, reported a case in which sulfanilylguanidine was administered preceding resection of the right colon and anastomosis between the terminal ileum and the transverse colon. There was an amazing drop in the bacterial count during the preoperative preparation period and there was no evidence of infection in the wound. Frank H. Lahey, Boston, asked if there have been any contraindications or any evidences of toxicity in the use of the drug.

In closing, Firor stated that, with reference to the degree of absorption, it has been found that the blood level concentration ordinarily runs between 2 and 4 mg. per cent, and in only two instances did it go over 5 mg. per cent. The dosage was experimented with in this group of patients, and at present it is felt that 50 mg. per kilogram of body weight every eight hours for a week before operation and a week after operation is perfectly safe. It has been found in some experimental work that far better results are obtained by giving the drug at eight-hour intervals than more frequently or in a single dose. Evidence of toxicity or contraindications to the use of the drug have not been found. Marshall has been employing the drug in cases of bacillary dysentery, with astounding results when it is given in the first three days of illness. He added that a report on this use of the drug would appear in the January issue of the *Bulletin of the Johns Hopkins Hospital*.

29. Frank S. Johns, Richmond, Va.: **Recurrent Carcinoma of the Rectum.** Johns reported the case of a male patient who had a "recurrence" of carcinoma in the region of the stoma, which followed a Kraske operation performed fifteen years previously for a grade II carcinoma. Examination of the specimen, removed by combined abdominal and posterior resection at the second operation, revealed the carcinoma to be of grade III, but the pathologist reported "a striking resemblance in the cell morphology to the previous growth" and that "it was probably of similar cell origin." A year and a day have now passed since the second operation and on recent examination the patient, now 42 years old, seems to be in good health.

30. Frederick A. Collier, Ann Arbor, Mich.: **Regional Lymphatic Metastasis of Carcinoma of Colon.**—Collier presented the results of observations made on clarified specimens of colon and attached mesentery in respect to the occurrence and distribution of metastases. By this method, employed by associates of his, a much higher percentage of nodes was demonstrable. It has been possible to demonstrate fifty-two lymph areas per specimen instead of an average of fourteen by older methods. In 46 cases there were 28 with metastases, an incidence of 60.87 per cent. By means of charts of various parts of the colon, areas and directions of metastatic spread were indicated. Frequently, no correlation is found between the size of the colon tumor and the presence or extent of metastases. Likewise, in his series there was no correlation between the duration of the disease and the degree of metastasis.

Metastases, however, do parallel the increasing grade of malignancy of the tumor. Many metastatic nodes are not palpable, and the size of lymph nodes is no index of metastasis. Therefore, operative procedures must be based on anatomical knowledge rather than on detectable lymph nodes.

**31. Henry W. Cave, New York City: Mortality Factors in the Surgical Treatment of Ulcerative Colitis.**—The author has done 90 operations on 50 individuals, with a mortality rate of 22 per cent. In 1939, 59 people in New York City died of ulcerative colitis. The horror of having a terminal ileostomy causes disastrous delays in many cases. Hemorrhage and peritonitis are the direct causes of death. Recently, sulfanilamide, administered orally, has been employed in the management of these cases. Ulcerative colitis is a cyclic recurring disease, and it is often difficult to choose the proper time for surgical intervention. In selecting cases for operation, judgment is based on a consideration of whether or not the disease is undergoing uninterrupted progression, or whether there are remissions, either one of which circumstances constitutes indication for surgical intervention. Operation should be done during a period of quiescence. Preoperative medical observation and preparation are very important.

**Discussion:** **Frank Lahey, Boston,** stated that at the Lahey Clinic there have been 280 cases of ulcerative colitis, with 80 complete colectomies and 3 deaths. There were 14 colectomies with no deaths. There have been 5 restored ileostomy cases. In emergency or extremely ill cases only a loop type of ileostomy is performed; whereas, in elective cases an end type ileostomy is done. Lahey felt that any individual who has had two episodes of colitis should have an ileostomy. Lahey felt that not every case with a rigid colon is a candidate for colectomy. In order to avert pulling of the intestine into the abdomen, he advocated fixation of the mesentery to the peritoneum.

**Discussion:** **Harvey B. Stone, Baltimore,** noted that sulfanilylguanidine has been tried in a few cases of ulcerative colitis, and it is believed that the drug is of no value in the treatment of the basic lesion. However, it is considered to be of value in preoperative preparation in order to reduce the number of the colon group organisms. Stone also emphasized the importance of early ileostomy.

**32. Harvey B. Stone, Baltimore: Results With the Fascia Plastic Operation for Anal Sphincter Repair.**—The present report is based on 30 operations performed by various surgeons in Baltimore. The author reviewed the operative procedure which he has previously described. The operation may be employed to advantage in certain cases of anal fistula, in congenital abnormalities, following operation for hemorrhoids in which there has been loss of sphincter function, following rectal cancer operations, in certain cases of perineal lacerations, prolapse of the rectum, and congenital megarectum, following trauma, and in some cases of anal ulcer. The results have been excellent in 12 cases (40 per cent), good in 9 cases (30 per cent), fair in 5 cases (16.6 per cent), and unsatisfactory in 4 cases (13.3 per cent). When the gluteal muscles are also impaired, as in certain cases of spina bifida, the operation is of no value. The author emphasized the importance of a period of training in order that the individual might gain full benefit from this operation. Since it is necessary to train the patient to contract the gluteal muscles, it is unreasonable to expect good results in very young children, or in adults with low mentality. The procedure, in case of a primary failure, may be repeated.

Discussion: Harry Warthen, Richmond, Va., presented the case of a child in which the procedure described by Stone had been employed. The results were very satisfactory. Deryl Hart, Durham, N. C., reported a case of a patient with congenital incontinence of feces in which strips of fascia were employed to bridge the ends of a deformed sector of the anal sphincter.

33. W. L. Estes, Jr., Bethlehem, Pa.: **End Results in the Treatment of Inguinal Hernia by a Fascia-to-Fascia Rectus Sheath Closure.**—The factors which influence the recurrence of hernias include the age of the patient, the type of the hernia, the character of the patient's tissue, and the type of operation. After discussing various types of operations for hernia, the author described in detail the procedure which he employs. Following high ligation of the sac and closure of any defect in the transversalis fascia, a flap of rectus abdominis muscle sheath is raised and then sutured to Poupart's ligament. The line of suture should not be continued above the normal level of the internal inguinal ring, as such a procedure will cause pressure on the cord and testicular atrophy will result. The outer flap of the external oblique fascia is sutured to the medial edge of the defect produced in the rectus abdominis muscle sheath. The procedure has been employed in 394 cases, 86 per cent of which have been followed up. All but 16 of the cases followed up were seen and examined. There were 4 recurrences within a year following operation. In 317 indirect hernias there was a recurrence of 0.4 per cent. In 80 direct hernias there was a recurrence of 2.77 per cent; and in 19 recurrent hernias there was a recurrence of 12.5 per cent. In a total of 416 operations there was a postoperative recurrence in 5, or an average of 1.2 per cent.

34. Charles R. Robins, Richmond, Va.: **Why Inguinal Hernia Recurs.**—The anatomical features, and methods of diagnosing hernias were reviewed. Direct and indirect hernias are frequently present in combination. Most recurrences occur within one year. The shutter action of the flat muscles of the abdominal wall was discussed, as was also the thick ligamentous fascia which runs along the top of the pubic bone. The author advocated the use of fascial sutures.

Discussion: Bradley Coley, New York City, felt that the many methods advocated for the repair of hernia evidence the imperfect results frequently observed following operations for hernia. He advocated the use of nonabsorbable suture material, particularly silk, which averts wound infection and rupture. Operations which involve taking a bite in muscles in the region of the internal ring interfere with the shutter action of the muscles in that region. Many slight direct bulges may best be left alone. Harold Foss, Danville, Pa., felt that simple types of operations are generally best. He prefers silk or cotton to fascia. In addition to the use of nonabsorbable suture material, Foss considered that adequate obliteration of the inguinal canal was important in effecting a cure in hernia. Willard Bartlett, St. Louis, discussed the occurrence of atrophy of the testicles following hernioplasty. Because of the possibility of bilateral atrophy following operation, the advisability of operating upon but one side at a time should be considered. G. B. Rhodes, New York City, described an operation in which a triangular flap of rectus sheath is employed. The flap is passed through a slit in the external oblique fascia and then sutured to Poupart's ligament. Frederic Baneroff, New York City, has employed an operative procedure which represents a modification of the type of operation performed by Estes. Believing that the bladder, when the patient is in the erect position, plays an important part in the recurrence of hernia, he advocated exposing the bladder and drawing it medially by means of sutures

through the bladder and through the rectus abdominis muscle sheath. Donald Guthrie, Sayre, Pa., voiced his favorable experience with the use of cotton as suture material.

35. J. Shelton Horsley, Richmond, Va.: Resection of the Duodenum for Tumor of the Ampulla of Vater.—Techniques which have been developed for the excision of the second portion of the duodenum and the head of the pancreas were reviewed. Horsley stated that the Whipple procedure has been modified so that the common duct is anastomosed end-to-side to a loop of jejunum, and that a jejunojejunostomy is performed in addition to the performance of a gastrojejunostomy and excision of the duodenum and pancreas. A case was reported in which Horsley resected part of the second portion of the duodenum along with a portion of the pancreas on account of a tumor located in the region of the ampulla of Vater. The tumor was a fibroadenoma. Although wound healing, as revealed at autopsy, was quite satisfactory, the patient died of uremia.

36. R. Arnold Griswold, Louisville, Ky.: Perforated Peptic Ulcer.—This report is based on 111 cases. There was a ratio in this series of white to colored patients of 4:3. Only 65 per cent of the patients vomited after perforation had occurred. Only 3 were in shock, as indicated by a blood pressure determination, although a clinical appearance suggesting shock was present in other cases, and the author drew attention to the fact that pallor may be misleading in suggesting the existence of shock in ruptured ulcer cases. Seventy-three per cent of x-rays revealed air beneath the diaphragm. All patients who were distended at the time of operation died. Nine of the 111 patients were not operated upon because they were first seen long after perforation. The author has discontinued the use of spinal anesthesia because of 2 deaths which followed its administration. He prefers a transverse abdominal incision and he advocated simple closure of the perforation with two rows of sutures. Sulfanilamide is instilled into the peritoneum and into the wound in some cases. Ordinarily, no intraperitoneal drainage is attempted. Silk sutures are employed for closure of the wound in the abdominal wall. It was considered that the presence of streptococci in the peritoneal cavity influences the mortality following perforated peptic ulcer.

Discussion: Ambrose H. Storck, New Orleans, La., presented some of the findings in a study recently completed at Tulane University by Ochsner and DeBakey, based on a review of approximately 23,000 cases of perforated peptic ulcer, as well as some findings revealed from a review of records at the Charity Hospital at New Orleans. The incidence of perforation in peptic ulcer in the cases collected from the literature was 13.2 per cent; whereas, in the Charity Hospital cases it was 8.09 per cent. There has been an increase in recent years in the percentage of perforation of peptic ulcers in the Charity Hospital series. Whereas perforating duodenal ulcer occurs most frequently in the ages between 20 and 40 years, the peak incidence of perforation of gastric ulcer is in individuals about 50 years old. In 11,305 cases in which the location of the perforation was accurately recorded, 51.2 per cent were duodenal, 38.9 per cent were gastric, and 9.8 per cent were "pyloric." There was a constant direct relationship between the death rate and the age of the patient, and the mortality increased progressively in relation to the number of hours elapsed between the time of perforation and the time of operation. Although the mortality was highest in the group of cases in which local anesthesia was employed, this type of anesthesia was frequently employed in cases of long duration or in poor risk patients. The relatively low mortality when spinal anesthesia was administered suggests that this type of anesthesia is preferable to general anesthesia. The mortality following various operations was as follows: simple closure, 25.9 per

cent; closure plus gastroenterostomy, 20.4 per cent; excision plus closure or pyloroplasty, 15.9 per cent; gastrectomy, 13.5 per cent. The relatively high mortality following simple closure no doubt was due to the employment of this procedure in the majority of patients who were in poor condition. The very low mortality following gastrectomy reflects the skill and experience of the relatively few surgeons who employed this procedure. Not only is excision of the ulcer plus closure or pyloroplasty effective as a means of meeting the problem of perforation, but the follow-up results after this type of procedure are very satisfactory. Relatively poor results following simple closure might be averted if more of the patients on whom this procedure is employed were properly instructed in regard to postoperative, dietary, and general hygienic regimen. In 942 cases in which the cause of death was definitely stated, peritonitis was found in 57.1 per cent, pulmonary lesions were present in 20.7 per cent, and other causes were reported in 22.1 per cent. Robert Rhodes, Augusta, Ga., reported a case of duodenal ulcer in which there was no air bubble demonstrable by x-ray. Following simple closure of the perforation, this patient subsequently had two perforations at points distal to the site of the first perforation. Albert Singleton, Galveston, Tex., discussed the occurrence of perforation of peptic ulcers in infants. Recently, Singleton operated upon a 14-hour-old infant, and he has operated upon another infant 3 days old. There are many cases of early perforation of peptic ulcer recorded in the literature, including one case in which perforation occurred in utero. John M. T. Finney, Jr., Baltimore, illustrated a familial tendency or predisposition to ulcer, stating that he had operated upon three brothers for perforated ulcer. Two of these patients gave no ulcer history. All of them lived. Finney referred to the use of the round ligament of the liver as a plug in cases in which simple closure is done. Joseph Donald, Birmingham, Ala., stated that excision of the ulcer followed by pyloroplasty has been used at the Hillman Hospital for the past several years with very gratifying results. He believes that the use of the transverse abdominal incision reduces the incidence of wound disruption.

In closing, Griswold referred to the employment of the Gatch procedure of folding nonindurated stomach and duodenal tissue over the site of perforation.

37. George Curtis, Columbus, Ohio: *Mediastinal Ganglioneuroma*.—Ganglioneuromas may occur throughout the body, but they are mainly found along the course of sympathetic nerve trunks. Most frequent sites are in the neck, thorax, abdomen, and pelvis. The author also discussed the closely related tumors of the adrenal gland. Mediastinal ganglioneuromas are uncommon, but the frequency with which they are recognized is increasing because of more x-ray examinations, and advances in thoracic surgery which permit exploration as well as removal of these tumors. The case upon which the author's present report was based was that of a 35-year-old nurse. The tumor was successfully removed by thoracotomy. Preoperative recognition of the presence of the tumor was the result of routine x-ray examination of the chest, as there were no symptoms. Preceding the removal of the tumor, preparatory pneumothorax was done. Gross examination of the specimen revealed myxomatous areas, fibrillar areas, and hemorrhagic areas. Microscopic examination revealed it to be a ganglioneuroma. Of the 200 ganglioneuromas so far reported in the literature, about 30 have been mediastinal.

Discussion: Julian Moore, Asheville, N. C., spoke of extrapulmonary intrathoracic tumors. He deplored the fact that many patients with such tumors are not given the benefits which may be afforded by modern chest surgery. All these tumors were considered by him to be potentially malignant. Diagnostic procedures include pneumothorax, bronchoscopy, and therapeutic tests by means of x-rays. In advocating thorax, bronchoscopy, and therapeutic tests by means of x-rays. In advocating cyclopropane or ether as an anesthetic, Moore remarked that, although positive pres-

sure anesthesia is necessary, he does not believe that intratracheal anesthesia is necessary. In order to guard against infection and emphysema, he believes that a catheter should be inserted and suction applied postoperatively.

**38. G. V. Brindley, Temple, Tex.: Carcinoma of the Fundus of the Uterus.**—This report is based on 92 cases. The ratio of uterine carcinoma to uterine sarcoma is 6:1. Eighty per cent of the patients were past 50 years of age. Abnormal bleeding is the most common symptom. Carefully performed curettage is the only accurate diagnostic method. All fibroids should be carefully examined immediately following their removal because some will be found to have areas of carcinoma in the fundus of the uterus. The highest percentage of cures in carcinoma of the fundus of the uterus is obtained by means of hysterectomy supplemented with radium or x-ray. The hospital mortality in the present series was 1.1 per cent. The degree of malignancy is low in two-thirds of the cases, and 79 per cent remained cured five years or longer by means of surgery and irradiation. Only about 40 per cent of five-year cures follow irradiation alone. The low-grade growths tend to occur in the younger group of women.

**39. Curtis H. Tyrone, New Orleans, La.: Operative Repair of Uterovaginal Descent.**—Operations for this condition were done as early as 1507, but not until much later were they generally performed. The author reviewed the various methods which have been employed for the treatment of uterovaginal descent. He discussed the application of the methods rather than the details of any particular operative procedure, although essential anatomy and brief descriptions of operative procedures were discussed. Prolapse may occur in virgins and in nulliparous women, but usually this condition is the result of prolonged labor. Indications for the employment of the interposition operation, the Manchester-Fathergill operation, and vaginal hysterectomy were reviewed. The author considered vaginal hysterectomy to be one of the most satisfactory operations, as it eradicates the associated cervical and endometrial disease. He also discussed the Le Fort operation, and spoke of the removal of the prolapsed cervical stump which may follow supravaginal hysterectomy.

**Discussion:** Edward Richardson, Baltimore, agreed that carcinoma of the fundus usually should be treated by means of radiation and surgery. He drew attention to the striking fact that there is a frequent time waste between the appearance of symptoms and the operative attack. If improved results are to be obtained in the management of this condition, such a time waste must be reduced. He reiterated the fact that no single operation is satisfactory for all cases of uterovaginal descent. Emil Novak, Baltimore, in addition to discussing the use of both radium and surgical methods in the treatment of carcinoma of the fundus, emphasized the importance of microscopic examination. Benign hyperplasia, although histologically quite distinct, is sometimes mistaken for adenocarcinoma. In the repair of cystocele it is important that the suburethral space be filled in or closed, and he referred to a triangular suture by which this might be accomplished. Perineorrhaphy does not cure rectocele, due to rectovaginal septum tears or stretching. Donnell B. Cobb, Goldsboro, N. C., spoke of postvaginal hernia and prolapse of the floor of the cul-de-sac of Douglas. This condition must be recognized and corrected if cure of the total condition of prolapse is to be accomplished. Unfortunately, almost half of the instances in which this condition exists are not recognized, although the diagnosis can readily be made by means of proper rectal examination. Treatment of this condition is similar to the treatment of other hernias. John Burch, Nashville, Tenn., discussed the occurrence of endometrial emboli following curettage. The employment of suction or punch methods permits diagnosis without the danger of dissemination of uterine carcinoma beyond its original location. He concurred with Cobb in his

belief that postvaginal hernia is more common than is generally recognized, and he advocated routine exploration of the cul-de-sac in cases in which vaginal hysterectomy is performed.

40. Fred Krock, Fort Smith, Ark.: Arrhenoblastoma of the Ovary, Further Remarks.—Only in recent years has it been fully appreciated that tumor tissue may function in a manner similar to its related normal tissue. To illustrate this point, the author cited the secretion of bile by a hepatoma which had metastasized to the brain. There are various types of arrhenoblastomas; some are associated with great, while others are associated with little, virilism, the variations in manifestation being related to the degree of differentiation of the tumor. The author reported further on a previously presented case in which femininity returned six weeks after the removal of the tumor. Subsequent operation, performed because of pain of which the patient complained, revealed two tumor nodules, and examination of the tissue removed at operation revealed cartilage in the recurrent growths. The theories which have been advanced to account for the occurrence of arrhenoblastomas were reviewed, and included the following: (a) hermaphroditism, (b) gonadal protective effect, (c) latent male elements, and (d) teratomas. The frequent finding of various types of cells in a single specimen supports the teratomatous theory. Other masculinizing ovarian tumors which the author considered in the course of his presentation included: (a) granulosa cell tumors, (b) aberrant cortical tumors, (c) embryonal carcinoma, (d) lutein cell tumors, (e) true sarcoma, and (f) dermoid tumors. Krock considered that arrhenoblastomas may represent one-sided teratomas.

Discussion: Emil Novak, Baltimore, remarked that Krock and his associates were the first observers in this country to describe arrhenoblastoma. In none of the three cases of his own, nor in the eight other cases in his laboratory, has Novak found evidence indicating a teratomatous nature of arrhenoblastoma. He believes that these tumors are related to the ovarian medulla or to the suprarenal cortex, both of which exert some masculinizing effects. Novak also remarked on the variation in the histologic appearance of arrhenoblastomas. Hirsutism alone is not an evidence or syndrome of masculinization.

## REPORT OF THE MEETING OF THE ANESTHETISTS' TRAVEL CLUB, BOSTON, MASS., OCT. 7, 8, and 9, 1940

RALPH T. KNIGHT, M.D., MINNEAPOLIS, MINN.

**E**IGHTEEN members of the Anesthetists' Travel Club met in Boston Oct. 7, 8, and 9, with **Lincoln Sise**, **Philip D. Woodbridge**, and **Sidney Wiggin** as the hosts. Four members from Canada were able to attend: **Wesley Bourne** and **Charles Stewart**, from Montreal, and **Charles Robson** and **W. E. Brown**, from Toronto.

The mornings were spent at clinics at the New England Baptist, New England Deaconess, and Faulkner Hospitals. The outstanding anesthesia theme at all of these hospitals was undoubtedly the combined use of various anesthetics and methods to the advantage of the patient and the surgeon. Such combinations as intravenous and inhalation, spinal and inhalation, and spinal and intravenous anesthesia, were demonstrated with various types of cases as providing very adequate operative conditions together with the least unpleasantness to the patient and the least disturbance of his physiology.

In abdominal surgery, especially procedures upon the stomach and gall bladder, continuous or fractional spinal anesthesia was demonstrated. Some of these patients were also lightly anesthetized with cyclopropane or intravenous pentothal, barely into the zone of unconsciousness, to prevent tire and nausea. A very small additional dose of spinal anesthetic was occasionally added. Relaxation was excellent and controllable; general anesthesia, minimal. A hysterectomy was also performed under continuous spinal anesthesia. It was possible to start with a much smaller dose than would otherwise have been deemed necessary and the final total turned out to be less than would have been administered in a single dose.

Intratracheal cyclopropane was demonstrated for chest surgery, and intratracheal air-ether insufflation for brain surgery and major oral and head surgery.

Wiggin also especially stressed, in his clinical demonstrations at Faulkner Hospital, the combined use of spinal and other anesthetics in "balanced" anesthesia. In a seminar he presented a large number of anesthesia records, classified into groups, to demonstrate the control of blood pressure under spinal anesthesia and the management of anesthesia for bad-risk patients.

Tuesday afternoon was spent at Massachusetts General Hospital with **Henry K. Beecher** who demonstrated intratracheal ether-oxygen anesthesia for a pneumonectomy and led a round-table presentation and discussion on **Controversial Problems of Anesthesia for Thoracic Surgery**. Beecher advocates the use of ether rather than other anesthetics, and the attachment of a mask to the tracheal tube to provide a gas-tight connection rather than the use of an inflatable cuff or oropharyngeal packing. He advocates the former because of its margin of safety and the latter because of the desire for drainage of secretion around the tracheal tube in addition to aspiration through it.

Wednesday afternoon was spent at the Massachusetts Institute of Technology with **J. W. Horton** who has done a large amount of research on the explosion hazard. He demonstrated the explosibility of various mixtures of gases and showed that certain proportions of oxygen, ethylene, and cyclopropane, with the oxygen relatively high and the other gases in such proportions as to produce any

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plane of anesthesia, are noninflammable and will even quench a flame. No technique had as yet been worked out to insure the continuance of the mixture within the required limits in the actual clinical administration of anesthesia. Horton also demonstrated the prevention of accumulation of dangerous charges of static electricity by the use of metal intercoupling with interposed resistance and by the use of conductive rubber shoe soles, apparatus parts, and flooring.

At the Lahey Clinic Building on Monday afternoon the anesthesia staff presented an excellent program. Woodbridge gave their statistics for 1939. Sise reviewed intravenous anesthesia and gave many excellent points concerning the principles, precautions and management. U. H. Eversole and F. H. Lahey discussed post-operative bronchoscopic aspiration therapy. There was a symposium on all types of spinal anesthesia. In another discussion stress was placed upon the anesthetist's preoperative visit for the coordination of the preanesthetic medication with the patient's physical and mental status, the anesthetic to be selected, and the operation to be performed.

## REPORT OF THE TWENTY-SIXTH ANNUAL MEETING OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA, CLEVELAND, OHIO, DEC. 2-6, 1940

C. N. BORMAN, M.D., MINNEAPOLIS, MINN.

*(From the Department of Radiology and Physical Therapy of the  
University of Minnesota)*

THE annual meeting of the Radiological Society of North America was characterized by the attention given to matters of military interest. W. Herbert McGuffin, of Calgary, Canada, reported on a survey of recruits for the Canadian army, basing his observations on single film examinations of the chest of 10,000 enrollees. The chief interest centered about the basis of rejection and the classification of those examined. Recruits were placed in four classes: (1) those fit for full-time military service, (2) those fit for restricted military duty, (3) those fit for service in Canada alone, (4) those totally unfit for any military duty. Briefly, congenital, valvular, or hypertensive heart cases were placed in Class 4. Evidence of fibrotic tuberculosis under 21 years of age or of pneumoconiosis also placed the recruit in Class 4. Surgical or chest consultants are frequently called in to determine classification in more questionable lesions. Cases of active tuberculosis are not allowed to return to work in their respective communities without first undergoing observation and supervision, because of the potential menace to public health.

During the Symposium on War-Time Roentgenology which occupied one-half of a day's session, Major Alfred A. DeLorimier discussed in detail the new army portable x-ray equipment, with complete plans for x-ray service from evacuation units to the base hospital centers. Excellent apparatus has been designed and is being made, with the mobile units permitting complete fluoroscopic and film examination in conjunction with the surgical units. An efficient foreign body localization apparatus is a part of the x-ray setup and a demonstration of extremely rapid localization, as will be universally employed, was a feature of the army apparatus display. Since portable processing tanks have been perfected, complete

film examination is available with all portable units. Present plans and equipment permit complete examination while the patient is on a stretcher, thereby avoiding moving of the wounded onto a table. Plans are being made for the use of low-voltage therapy in the evacuation or temporary centers. This may be an important adjunct to early surgical care of potential gas gangrene cases.

**Roentgentherapy in Cancer of the Breast Used Preoperatively or in Non-operated Cases** constituted the basis of a report by Maurice Lenz, of the Presbyterian Hospital, New York City. The possibility of complete cancer cell sterilization by this means appeared quite remote. Of 40 cases, 16 were shown to have distant metastasis at the time of surgery. A large number of cases, deemed surgically incurable, have received roentgen therapy alone, since survival rates probably are better than in those cases submitting to surgery even though admittedly incurable.

Late results in 33 cases of benign giant cell tumors of bone were reported by Traian Leucutia, of the Harper Hospital, Detroit. Eighteen cases had radiation therapy alone, and on the basis of the five-year end results this method was considered the one of choice. Disadvantages of surgical intervention are: (1) infection is not a rare surgical complication (it never occurred in the irradiated series); (2) filling in with bone after application of escharotics is often not satisfactory and reossification occurs faster in the irradiated group; (3) escharotics may act as irritants and result in late malignant degeneration. Most of the cases shown had good bone regeneration after a period of five to ten years and the anatomic and functional results were excellent. The method of therapy employed was that of repeated gradually decreasing doses, usually begun with a course of 525 r in air, with 200 kv. computed on the basis of a 20 by 20 cm. field. Usually 6 to 8 series, each dosage decreased by 10 per cent, extending over a period of two years, was employed. Especially good regeneration was noted in children. Restricted use of the extremity during treatment was recommended to obviate temporary bone decalcification, and possible secondary fracture. Discussants of the paper brought out the danger of not biopsying these lesions, since malignant sarcomas often mask the picture; also the danger of irradiating joints (epiphyses) of young children because of growth interference was emphasized. Cystic lesions about the knee joint were pointed out as being particularly prone to show malignant changes.

Paul A. Zahl, of the Memorial Hospital, New York City, discussed his experimental studies on the localization of lithium-containing dye in certain tumors in mice after intravenous injection. Since lithium atoms release tremendous energies, for surpassing the ionizing power of the electron, and since this violent release of energy occurs when the lithium atom captures "slow neutrons," the use of slow neutrons on lithiated tumors has been considered from the therapy standpoint. Analysis of the injected mice showed twice the concentration of lithium in the tumors as compared to surrounding normal tissue. Theoretically this will permit the release of three times as much energy in the tumor as in the normal tissue. One of the difficulties encountered has been the production of a high enough differential concentration of lithium between tumor and normal tissue; as a result the destructive effects cannot be localized to the tumor, unless it is in a readily accessible location. Another difficulty may also be encountered in obtaining proper slow neutron concentrations in the tumors.

**The Metabolism of Radioactive Phosphorus by Malignant Neoplasms in Human Beings** formed the basis of a report by John M. Kenney, also of the Memorial Hospital, New York City. Small "tracer doses" of radioactive phosphorus, orally administered, have been given to patients with lymphosarcoma, inoperable car-

phane of anesthesia, are noninflammable and will even quench a flame. No technique had as yet been worked out to insure the continuance of the mixture within the required limits in the actual clinical administration of anesthesia. Horton also demonstrated the prevention of accumulation of dangerous charges of static electricity by the use of metal intercoupling with interposed resistance and by the use of conductive rubber shoe soles, apparatus parts, and flooring.

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to fibrosis and tumor bed changes was emphasized. The more beneficial effect from radium applied after the external irradiation may be due to removal of infection in the cervix, since the presence of infection may produce a lessening of the degree of radiosensitivity of the tumor. Radium application by means of intracervical capsules and tubes in the fornices (colpostat) simultaneously in all possible instances appeared to be a recognized and preferable practice. Axel N. Arneson, St. Louis, indicated his best results were obtained in cases having had radium needle insertion and external irradiation applied simultaneously.

Max M. Peet, University of Michigan, discussed his experiences with ventriculography in brain tumor diagnosis. He stressed the value of determining the extent, location, and approximate size of the lesion, and indicated that this procedure is used in almost every case of brain tumor. A single posterolateral approach was advocated rather than the usual bilateral posterior trephining, and oxygen has replaced other substances as a contrast medium.

Gilbert Thomas, Minneapolis, Minn., emphasized the need for repeated bilateral retrograde pyelograms in the diagnosis and treatment of early renal tuberculosis. In most cases, because of the difficulty in proper preparation of the tuberculous patient, intravenous urograms are unsatisfactory for detecting the early lesion. The frequency of diffuse lesions by hematogenous spread means that the kidney should always be considered with suspicion in the presence of other distant lesions, such as bone or joint tuberculosis. A single negative pyelographic study does not rule out renal tuberculosis.

Claude S. Beck, Cleveland, Ohio, presented a cinematographic demonstration of lesions producing compression of the heart, in addition to his discussion of that subject. He prefers to class heart lesions in two large groups: extrinsic and intrinsic lesions. In extrinsic lesions, if the abnormality can be surgically corrected, the patient may be cured. Three chief extrinsic lesions producing interference with heart function as revealed by the pulse and blood pressure are: (1) angulation by adhesions, (2) torsion or rotation (dislocation), and (3) compression by fluid or scar tissue. His discourse concerned itself primarily with compression of the heart by scar tissue. Objection to the term "adhesive pericarditis" was voiced, since adhesions to the heart do not compress the heart, and in Beck's opinion do not in themselves interfere with heart action. Constrictive pericarditis or scar tissue, which may form on any chamber or chambers, results in actual compression, decrease in volume capacity, and in a characteristic and unmistakable clinical picture. The outstanding features are a small, quiet heart, evidence of venous pressure elevation and widespread pressure congestion (enlarged liver and spleen, ascites, edema, distention of veins of neck). A number of cases were demonstrated, the spectacular surgical procedures shown very clearly by means of motion pictures taken during the operations, and the final end results demonstrated on patients who have long since returned to work. Post-operative external drainage is not attempted.

Diaphragmatic Hernia of the Stomach was discussed by David Beilin, of Chicago. He stressed the increasing frequency of diagnosis and pointed out the importance of differentiating the true paraesophageal hernias from the true diaphragmatic congenital defects (foramina). These are often best shown in the lateral view. George Crile, Jr. (discussant), Cleveland, Ohio, pointed out that surgical repair is often not difficult; it is unfortunate that clinicians often do not consider surgical repair because of the impression that the surgical procedure is, in their minds, a formidable one. Crile believes the transpleural approach is usually not necessary. The "short esophagus" must be ruled out before contemplating surgery.

cinoma of the breast, and osteogenic sarcoma of bone. After five to seven days, biopsies were made of the lesions; the percentage of the phosphorus retained in relation to the amount given, after deducting 25 per cent for loss of excretion, was calculated. This again was reduced to terms of "equivalent roentgens" present in the particular tumor. In certain cases as high as 1,000 to 1,500 equivalent r could be demonstrated in the nodes of lymphosarcoma. Sizeable doses were also demonstrated in metastatic nodes of inoperable carcinoma of the breast. Osteogenic sarcoma apparently absorbed more than any other tissue, and it was stated that it may be possible to give from 3,000 to 4,000 equivalent r to the tumor and lymph nodes. What effect this would have on the patient was not stated, since the amount of radioactive substance that may be tolerated by the body as a whole is as yet speculative.

Carlton B. Pierco, Montreal, Canada, described a new roentgen finding which indicates the presence of fat and hemorrhagic fluid in certain traumatic fractures about the knee. In the supine lateral position a fluid level was demonstrated with what appeared to be gas above the fluid level. There was no evidence of skin puncture. Further investigation showed a fracture of the head of the tibia with liberation of fat from the bone marrow, producing a layered shadow over the hemorrhagic fluid. Accordingly, in lateral films made in the supine position this layering phenomenon is due to fat and fluid in the bursae and indicates the presence of an intra-articular fracture, even though the fracture line itself may not be visible.

A symposium on *Methods in Irradiation Treatment of Carcinoma of the Cervix Uteri* was participated in by R. R. Newell, Stanford University, R. S. Stone, University of California Medical School, and S. T. Cantrel, Seattle, Wash.

In Stage I (League of Nations) lesions, if and when a case can be so classified, radium alone was recommended. Stone suggested surgical removal later if the case is operable. In the remaining stages (II, III, IV) external high voltage irradiation followed by radium application was generally agreed upon. It was emphasized that preliminary external irradiation was primarily designed for parametrial involvement. The advantage of using x-rays first was attributed to the favorable effect on infection and hemorrhage and to the reduction in size of the tumor and cervix, thereby permitting more effectual radium application. In all instances radium was relied upon to control the primary cervical lesion, but was not considered effectual for the parametrial region. The great danger of error in classifying Stage I cases (lesion localized to cervix) was pointed out by Stone; he quoted Taussig's operative figures wherein 25 to 33 per cent of so-called Stage I cases were found to have metastatic node involvement. Likewise, in Stage II and III cases 45 to 50 per cent and in Stage IV cases 66 per cent had node involvement. The iliac and hypogastric nodes, obturator, ureteral, and sacral nodes may be considered primary and the more distance nodes as secondary. Five to twenty per cent of cases may have primary node involvement without any evidence of parametrial spread, and in 5 to 10 per cent of Stage I and II cases, there may be secondary node metastasis without evidence of primary node involvement. However, 90 per cent of Stage I and II cases have metastases limited to the primary lymph nodes. A proper selection of fields of irradiation includes all these areas so that in a full course of therapy these regions receive the maximum effect permissible and the highest salvage possible may logically be expected. The necessity for individualization of treatment in each case was stressed by the essayists and discussants. The interval between completion of external irradiation and radiation application received some consideration. Suggested intervals varied from "a few days" to within "a period of two weeks." If too long a period elapsed, the possibility of development of radioresistance due

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## Original Communications

### CHRONIC ABDOMINAL PAIN DUE TO HYPOGLYCEMIA

WITH A NOTE ON THE PATHOGENESIS OF NEUROTIC SYMPTOMATOLOGY

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*(From the Medical Clinic, Morrisania City Hospital)*

THIS report describes a group of five patients who had long histories of recurrent attacks of abdominal pain due to unrecognized hypoglycemia. All had undergone thorough investigations in which all possible procedures were employed with the exception of the glucose tolerance test. Laparotomy was advised as a last resort. Appendectomy was performed three times; cholecystectomy and herniorrhaphy, once each. However, pain recurred and when the patients returned with their original complaints it was thought that they were confirmed neurotics or that they had postoperative adhesions. In addition to the pain the patients had neurologic manifestations of hypoglycemia which were not accorded their proper significance. Such manifestations were headache, nervousness, dizziness, sweats, faintness, and syncope. No doubt the recital of such complaints by a patient with abdominal pain would serve to stamp him as a neurotic, a term which is much overworked in medicine. If such symptoms are interpreted as hypoglycemic manifestations the true nature of the syndrome will become clear. Two female patients in the group had headaches of such frequency and severity as to necessitate investigation for brain tumor. One of these patients went through encephalography twice.

Hypoglycemia as a cause of abdominal pain has been reported by various authors.<sup>1-6</sup> The most successful form of therapy has been the employment of low carbohydrate diets with increased protein and fat (carbohydrate, 75 to 100 Gm.; protein, 75 to 125 Gm.; fat, 100 to 150 Gm.). Between meals and at bedtime the patient is instructed to take a glass of milk or milk and cream or tomato juice, with a cracker and butter or cheese. Bedtime feeding is especially indicated in cases of nocturnal pain. Relief from pain may be attained after a few days or

William S. Altman, of Beth Israel Hospital, Boston, pointed out the value of **Fractional Cholangiography** in both immediate and postoperative roentgen examination of the common duct. He recommended the use of 3 to 5 c.c. of diodrast (40 per cent) with films made either on the operating table or later in the x-ray department. After an interval of ten to fifteen minutes a second injection, through the catheterized common duct, of from 10 to 15 c.c. is made, and films are again taken. The preliminary small injection often demonstrates filling defects that are obscured by larger amounts of dye, and similarly filling defects may be conclusively demonstrated with the larger amount that were indefinite with a small amount. In 78 per cent of cases this fractional method of dye injection has been of distinct value. The sphincter of Oddi appears to be best demonstrated with the small injection. Caution should be exercised in exerting pressure during injection, since spasm of the sphincter may be induced. Amyl nitrite inhalation is of value in determining temporary spasm, since relaxation commonly follows its inhalation.

**Clinical and Roentgen Manifestations of Gastrocolic Fistulas** was discussed by Max Ritvo and E. J. McDonald, of Boston. While the clinical picture often suggests the diagnosis, the roentgen demonstration of the fistulous tract by means of the barium meal or barium enema examination constitutes conclusive diagnostic evidence. The importance of an early conclusive diagnosis was stressed since the mortality is high unless prompt surgical intervention and correction supervenes.

The need for prompt recognition of the fact that **Intrathoracic Neurofibromas** are often benign, usually surgically removable lesions, which do not respond to irradiation therapy, and are first detected by means of posteroanterior and lateral roentgenograms of the chest, was stressed by Karl Kornblum and Howard H. Bradshaw, of Jefferson Medical College, Philadelphia. These lesions, which are usually closely associated with the spine and represent a frequent posterior mediastinal tumor, can often be conclusively demonstrated in chest film examinations, which is the most important single diagnostic procedure. He stressed the constancy of their posterior position. They may become malignant and should be extirpated completely whenever possible.

**Adrenal Tumors and the Use of Air Insufflation in Diagnosis** was discussed by Dr. George F. Cahill, of New York City. Two hundred cases having symptoms of adrenal tumor, in which air insufflation of the pararenal fascial space was done, were reported. By means of this contrast method, Cahill was able to demonstrate that the vast majority of these cases were not due to adrenal tumors. Large carcinomas of the cortex were clearly demonstrated in certain cases and smaller hormonal secreting tumors of the cortex were also shown. In the hormonal medullary tumors diagnosis even with air insufflation was difficult because of their slight density and the occurrence of the tumors in the ganglia outside the adrenal. The author reported no accidents due to air insufflation, but emphasized the possibility of accident if air insufflation is done in the large tumors in which extensive dilatation of veins is present. During the discussion it was brought out that a number of fatalities have resulted from air embolism following insufflation, but Cahill felt that these were due to poor selection of cases.

These investigators concluded that the hypoglycemia affects the central nervous system and stimuli reach the abdominal viscera through the vagus. La Barre and Destree<sup>9</sup> found that a fall to 75 mg. in human beings stimulated gastric contractions; whereas, a fall to 45 mg. caused gastric atony.

From such experimental data one may justifiably attribute abdominal pain and nervous symptoms in patients with hypoglycemia to the abnormal fall in blood sugar concentration. The fact that a low carbohydrate diet by overcoming such abnormal behavior in blood sugar regulation can prevent the attacks is further confirmation that such a mechanism is responsible for the pain. These patients usually have relief from pain on taking food. Such relief may be attributed to the rise in blood sugar that follows the ingestion of food. Spontaneous relief from pain may be attributed to the rise in blood sugar that follows the mobilization of glucose from liver glycogen by the liberation of adrenalin, a protective mechanism which comes into play at hypoglycemic levels.<sup>10</sup> It is generally accepted that symptoms, such as tremors, sweating, pallor, tachycardia, and palpitation, occurring during hypoglycemic episodes, are actually due to such adrenal-sympathetic activity and may be regarded as unpleasant side reactions accompanying the essential glycogenolytic action of adrenalin.

The pain in hypoglycemic patients may be generalized or localized. It may be localized to the epigastrium, to the right upper quadrant with radiation to the back and shoulder, to either of the lower quadrants, or to the lower half of the abdomen. Apparently in each patient the hypoglycemia has a tendency to stimulate the same group of neurons in the vagal nucleus, and the particular segment of the gastrointestinal tract (including the biliary tract) innervated by these neurons undergoes strong contraction, which may even become tetanic.

As long as the patients remained on a low carbohydrate diet they had no pain. Whenever they went back to their former high carbohydrate intake they usually had recurrence after several days. This is to be expected since it has been demonstrated that a high carbohydrate intake increases sugar tolerance with resultant lowering of blood sugar levels.<sup>11</sup>

It is not within the scope of this paper to enter into a detailed discussion of the mechanism whereby a low carbohydrate diet actually brings about higher blood sugar levels. However, some consideration of the explanations that have been offered is in order. When Harris first coined the term hyperinsulinism he implied that patients with this disorder suffered an extra discharge of insulin on the ingestion of carbohydrate rich foods, such discharge resulting in hypoglycemia. On a low carbohydrate diet such stimulation of the pancreas and hypoglycemia would be avoided. Since a low carbohydrate diet usually relieves the symptoms of hypoglycemia and since it actually brings about higher blood sugar levels, such an explanation seems tenable. Recently, Soskin and co-workers<sup>12, 13</sup> have shown that the rate of discharge of

weeks, because such a diet elevates and stabilizes blood sugar levels (Fig. 1).

As to the mechanism responsible for the abdominal pain, the experimental injection of insulin into normal human beings and dogs has yielded pertinent data. Bulatao and Carlson<sup>7</sup> injected twenty to forty units of insulin subcutaneously into dogs. When the blood sugar was between 80 and 70 mg. there was an increase in gastric tone and in the height and frequency of contractions, gradually developing into tetany. They state that "as the blood sugar falls to convulsion level the stomach motor mechanism usually shows alternate periods of atony and tetany,

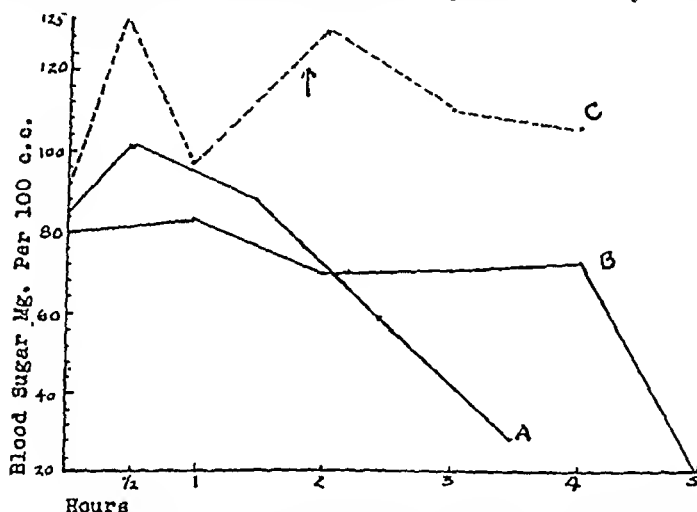


Fig. 1.—The effect of various meals on the blood sugar in a patient with chronic hypoglycemia whose chief complaint was severe headache. This patient is not included in the five cases reported in detail, but the response of the blood sugar to the various meals is typical of the response obtained in all patients investigated. Curve A shows the glucose tolerance after 100 Gm. of glucose; Curve B shows the course of the blood sugar after a high carbohydrate meal consisting of one orange, a bowl of oatmeal, two rolls, and a cup of sweetened coffee; Curve C shows the course after a low carbohydrate meal consisting of one orange, two eggs, one thin slice of bread and butter, a glass of milk to which 1 oz. of cream was added. About two hours after this meal the patient took a glass of milk.

the inhibition predominating." Quigley, Johnson, and Solomon<sup>8</sup> injected twelve to twenty units of insulin into normal fasting human beings. In about forty-five to ninety minutes following the injection subjective sensations, such as restlessness, weakness, hunger, and sweating, appeared. Soon there was increased gastric motility and as this became more marked subjective sensations with an "uncomfortable feeling of tension or pressure or pain referred to the stomach" often accompanied by lassitude or weakness appeared. Headache, nervousness, dizziness, vasomotor instability, irritability, and ill temper may appear. Subjective symptoms passed off after the subjects took fruit juice. They observed that "in persons with more stable nervous organization strong hunger may be present without the other accessory phenomena except hyperexcitability, and, conversely, in some persons the feeling of weakness and headache may be so marked as to crowd out the hunger pangs."

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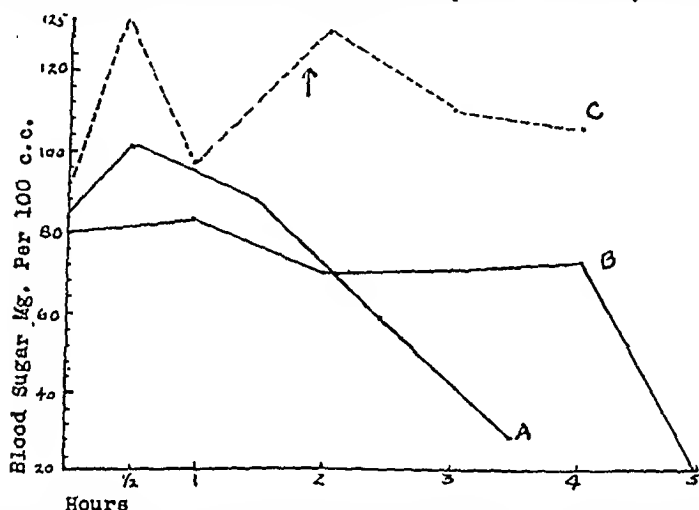


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the inhibition predominating." Quigley, Johnson, and Solomon<sup>8</sup> injected twelve to twenty units of insulin into normal fasting human beings. In about forty-five to ninety minutes following the injection subjective sensations, such as restlessness, weakness, hunger, and sweating, appeared. Soon there was increased gastric motility and as this became more marked subjective sensations with an "uncomfortable feeling of tension or pressure or pain referred to the stomach" often accompanied by lassitude or weakness appeared. Headache, nervousness, dizziness, vasomotor instability, irritability, and ill temper may appear. Subjective symptoms passed off after the subjects took fruit juice. They observed that "in persons with more stable nervous organization strong hunger may be present without the other accessory phenomena except hyperexcitability, and, conversely, in some persons the feeling of weakness and headache may be so marked as to crowd out the hunger pangs."

glucose from the liver is an important factor in the regulation of blood sugar levels. During the fasting state the blood sugar is derived wholly from the breakdown of liver glycogen. These workers found that when glucose was injected intravenously into a dog the liver output of glucose was inhibited and was not resumed at its usual rate until the blood sugar level had fallen to the previous fasting value. They further found that the greater the amount of glucose injected, the greater the inhibition of liver output. Further, if the inhibition was great enough the resumption of liver output may be delayed long enough to permit the blood sugar to fall to hypoglycemic levels. These workers also showed that such hypoglycemia was not due to an extra discharge of insulin.

Applying these experimental findings to patients with chronic hypoglycemia one may state that the ingestion of carbohydrate rich foods inhibits the liver output of glucose to such an extent as to bring about hypoglycemia. On a low carbohydrate intake such suppression of liver output is avoided and subsequent hypoglycemia prevented. During the fasting state the blood sugar is maintained by the breakdown of liver glycogen. It is obvious that the amount of glycogen stored in the liver will determine the amount of glucose liberated into the blood stream and the ultimate blood sugar level. A glycogen poor liver will thus be an important factor in the production of hypoglycemia.

It has also been established that tissues consume oxygen in proportion as they utilize glucose. This is especially so in the case of tissues with respiratory quotients of unity, such as the brain, which burns glucose practically exclusively for energy purposes. Dameshek, Myerson, and Stephenson<sup>14</sup> found that during insulin hypoglycemia in man there was a diminished oxygen consumption by the brain. Himwich and Fazekas<sup>15</sup> found that during insulin hypoglycemia in dogs there was a considerable fall in the oxygen consumption of the brain. Holmes,<sup>16</sup> Dickens and Greville,<sup>17</sup> and Wortis,<sup>18</sup> using the Barcroft-Warburg technique, found that the oxygen consumption of excised pieces of brain, spinal cord, heart, testis, kidney, and spleen fell as the amount of glucose in the nutrient medium was reduced. During hypoglycemia, in patients with this disorder, there will be an asphyxia of the brain of mild, moderate, or severe degree, depending on the degree of hypoglycemia. This reduction in oxygen consumption of the brain will readily explain the many and varied neurologic and so-called neurotic symptoms associated with hypoglycemia.

Fortunately hypoglycemia and its symptoms are reversible. However, fatal cases have been reported and cerebral lesions, especially hemorrhages, have been observed.<sup>19</sup> I mention this matter of hemorrhage because patients with hypoglycemia show a tendency to bleed, manifest clinically as epistaxis, the coughing-up of clots, coffee-ground vomitus, tarry stools, and occasionally frank rectal bleeding. Such bleeding disappears when treatment for the metabolic disorder is instituted. The bleeding is capillary in origin, although it may be profuse at times.

The capillary wall itself must suffer some injury as a result of the metabolic disturbance. Increased capillary permeability with escape of fluid into surrounding brain tissues may explain the headache of hypoglycemia. The relief from headache frequently obtained with coal-tar drugs, such as aspirin, may be due to the fact that one of the effects of such drugs is their ability to raise the blood sugar.

#### CASE REPORTS

CASE 1.—S. P., white male, aged 41 years, first attended the medical clinic in July, 1936, because of frequent attacks of abdominal pain of two months' duration. He had pneumonia at 9 years of age and gonorrhea at 16 years of age. He had a tonsillectomy in 1934 for frequent sore throats. In 1935 a urethral stricture had to be dilated. He was married, with a wife and four children living and well. He was a laundry worker. He smoked about ten cigarettes a day and took alcohol rarely.

In May, 1936, he began to have almost daily attacks of right-sided abdominal pain radiating to the lumbar region, usually coming on between 4:00 and 6:00 A.M., waking him from sleep. The pain was severe, and he would get up and walk about the room for about one-half hour until relieved. Sometimes the pain did not subside until he ate breakfast. Epigastric burning, belching, and sour eructations, but no vomiting, often accompanied the attacks. He also gave a history of tarry stools. He visited the clinic at frequent intervals during the summer of 1936. General physical and neurologic examinations revealed no abnormalities. The blood Wassermann test was negative. Blood counts and urinalyses were normal. Roentgen examinations of the gastrointestinal, biliary, and genito-urinary tracts revealed no abnormality. He was admitted to the surgical ward for further observation on Sept. 12, 1936. On the ward he had his usual attacks of pain and, since no further clues as to etiology were uncovered, an exploratory laparotomy was performed on Sept. 29 under general anesthesia. At operation no organic disease was demonstrable and a normal appendix was removed. His postoperative course was stormy. On the second day he had signs of a right middle lobe pneumonia with much distention and cramps. On Oct. 3 the wound was found gaping with visible coils of intestine. On Oct. 4 he had an attack of unconsciousness without convulsions. He improved slowly thereafter, although he sweated much at night. He was discharged on the thirty-fourth postoperative day. His attacks of pain promptly recurred and he returned to the clinic at frequent intervals during 1936 and 1937. He was first seen by me in August, 1937, still complaining of his pains. In view of the negative physical, laboratory, roentgenologic, and operative findings I regarded him as a neurotic and prescribed placebos, but without improvement. The patient was of phlegmatic temperament and not likely to be neurotic. In December, 1937, he complained of occipital headache, sweats, and attacks of faintness. These complaints were not of recent origin but had not been stressed by the patient because they were overshadowed by the abdominal symptoms. These nervous symptoms suggested hypoglycemic episodes and a glucose tolerance test on Dec. 22, 1937, revealed: fasting 54; one-half hour, 113; 1 hour, 92; 2 hours, 79; 3 hours, 35; 4 hours, 77. He was put on a low carbohydrate diet at once with feedings between meals and at bedtime. At the end of two weeks he reported that he had less belching and sour eructations and that the attacks of pain were fewer, less severe, and of shorter duration. At the end of four weeks he reported complete freedom from pain, belching, and eructations. The headaches and sweats became more infrequent and disappeared completely after two months. He had no more tarry stools. Now, after two years he continues symptom free.

*Comment.*—The occurrence of pain in this patient only during the early morning hours was due no doubt to the fact that the blood sugar reached its lowest level during the nocturnal fast. Blood sugar studies on other hypoglycemic patients with nocturnal symptoms have revealed that the occurrence of such symptoms coincides with low blood sugar levels at such times. Their occurrence at these hours may best be attributed to low liver glycogen reserves. As was stated previously, the blood sugar level during fast is maintained by the breakdown of liver glycogen. If such glycogen stores are low the blood sugar will not be maintained at normal levels; i.e., around 100 mg. The fact that it took about three weeks for his attacks of pain to cease completely and several weeks for his headaches and night sweats to disappear suggests that some profound bodily changes, such as an increase in glycogen stores, had to take place before blood sugar levels could be elevated and maintained at more normal levels. The attack of unconsciousness on the tenth postoperative day was undoubtedly a hypoglycemic episode, especially since the food intake was much reduced during this postoperative period and liver glycogen stores were further depleted. As to the evisceration I can only speculate. I have observed another patient, not included in this group, who had a blood sugar of 50 mg. during a tolerance test, and who two years before eviscerated following a cholecystectomy for gallstones. In view of the fact that cellular oxidations are reduced during hypoglycemia it is very likely that the metabolic processes concerned with growth and repair are not proceeding normally and the wound healing is delayed or defective. I have observed rapid healing of indolent infected wounds and ulcers following the institution of a low carbohydrate diet both in patients with frank hypoglycemia and in patients with more normal sugar levels. Benedict and Carpenter<sup>20</sup> have shown that there is a far greater oxygen consumption and heat production after the ingestion of protein rich foods than after the ingestion of carbohydrate rich foods.

CASE 2.—E. McC., white male, 50 years of age, first attended the medical clinic on May 22, 1937, complaining of frequent attacks of abdominal pain and vomiting of 1 year's duration. His past history revealed no major illnesses. He took no alcohol and smoked moderately. He had been employed as a restaurant worker. Because of loss of strength and marked tremors of the hands he was always dropping cups and glassware and had to quit his job.

The attacks of pain began in June, 1936. At that time they occurred at two-week intervals. As time went on the interval shortened so that by May, 1937, they were occurring every four to six days. The pain was generalized and severe, often radiating to the groins and testicles. Attacks lasted four to six hours, would disappear spontaneously, and would leave him prostrate. Vomiting always accompanied these bouts but did not relieve him. On questioning he said the vomitus sometimes resembled coffee grounds. During attacks he had a "dragging sensation" in the abdomen, felt faint, nervous, and had sweats. The attacks occurred only during the day and about three or four hours after a heavy meal. His appetite was good but he was afraid to eat since he noted that an attack was more

likely to follow a hearty meal. As a result he lost twenty-five pounds in twelve months' time. He also had had severe frontal headaches for several years.

Physical examination revealed a thin, nervous, apprehensive individual. Most of his teeth were missing. The thyroid gland was diffusely enlarged but not pulsating. There were coarse tremors of the outstretched hands, which were cold and damp. The heart and lungs were normal. The abdomen was soft and nontender. The liver edge was felt about two fingerbreadths below the right costal margin. There was a readily reducible incomplete left inguinal hernia of several years' duration. There were no abnormal neurologic signs. The clinical picture suggested hyperthyroidism but the basal metabolic rate was plus 1. The electrocardiogram revealed no abnormality. The blood Wassermann test was negative. Blood and urine examinations revealed no abnormalities. Roentgenologic and fluoroscopic examination of the gastrointestinal tract revealed no abnormality. He was hospitalized for further study on June 26, 1937. An attending physician made the following note: "The patient has a reducible left inguinal hernia, but I'm not sure that this is the cause of the abdominal pain, vomiting, and loss of 25 pounds." Two stool examinations were positive for occult blood. He had attacks of pain while on the ward. As a last resort, a hernia repair was advised, hoping to relieve him of his pain. He was operated upon July 9 under general anesthesia. His postoperative course was stormy. On July 20 his temperature rose to 104° F. with signs in the right chest of an early pneumonia. The wound became infected and he developed an ischiorectal abscess which had to be drained. He was discharged on the twenty-first postoperative day. His attacks of pain promptly recurred with the same frequency and intensity. He returned to the clinic at frequent intervals and was given various forms of medication without relief. He was first seen by me in January, 1938. Impressed with the history of headaches, nervousness, sweats, and feeling of faintness that accompanied the attacks of pain, a glucose tolerance test was done on Jan. 1, 1938. This revealed: fasting 75; one-half hour, 100; 1 hour, 95; 2 hours, 55; 3 hours, 45; 4 hours, 45. He was put at once on a low carbohydrate diet with between-meal feedings. In the ensuing four weeks he had only two attacks of pain, which were much less severe and of much shorter duration. After the fourth week the attacks ceased altogether and never recurred. At the end of two months he had gained 7 pounds and had fewer headaches, tremors, and sweats. His general nervousness and "shakiness" disappeared more slowly. Now, after two years, he has regained 20 pounds and has not had a single attack of pain in twenty-three months. He has been able to do hard manual labor without fatigue. Of course, he is still on a low carbohydrate diet.

*Comment.*—In contrast with Case 1 this patient had no nocturnal pain. His attacks would come on three or four hours after a "heavy meal," and for an individual on the relief roll a heavy meal contains much bread, potatoes, sugar, etc. In keeping with the explanation for the hypoglycemia offered by Soskin and his co-workers, one might say that the ingestion of the heavy meal suppressed markedly the liver output of glucose. The blood sugar values obtained in the tolerance test after 100 Gm. of glucose show a progressive fall after the first hour, reaching the low level of 45 mg. in the third and fourth hours. This paradoxical behavior of the blood sugar following the ingestion of 100 Gm. of glucose, in the present state of our knowledge, is best explained by the results of Soskin's work.

This patient's bouts of pain often lasted four to six hours before letting up. One might say that the adrenal-sympathetic mechanism was

deficient in that it failed to mobilize glucose from liver glycogen stores or that the glycogen stores were inadequate. Since his symptoms, such as tremors, nervousness, sweats, indicated adequate adrenal-sympathetic activity, it is more likely that the liver glycogen stores were depleted. Where liver glycogen stores are nearer normal, the bouts of pain should not last as long as six hours. The fact that patients, after being put on a low carbohydrate diet, have attacks of pain during the first few weeks, but of shorter duration and of lesser severity, suggests that the glycogen stores are being replenished so that when adrenalin is liberated in response to a fall in blood sugar the glycogenolytic response is adequate.

The patient's tremors, general nervousness, and sweats did not disappear completely until after five months, although they gradually lessened in severity after about two months. Since these symptoms are due most likely to sympathetic activity stimulated by the tendency to hypoglycemia, their disappearance depends on the restoration of the blood sugar to normal levels. The fact that the attacks of pain disappeared completely after four weeks suggests that a moderate elevation in blood sugar levels was sufficient to prevent pain but insufficient to relieve him of the nervous symptoms. It thus becomes evident that profound bodily changes must take place in order to bring about normal blood sugar regulation, and in some patients these changes can be accomplished only after several weeks or months.

This patient's postoperative course was also stormy. He had a right lower lobe pneumonia and a wound infection and developed an ischio-rectal abscess which had to be drained.

The change in the physical and mental status in this patient after a year was most remarkable. The transformation from a thin, nervous, "jittery," apprehensive individual, incapacitated by pain and weakness, to a buoyant, robust, willing worker was most gratifying.

CASE 3.—S. R., white male, 36 years of age, single, was first seen in April, 1938, complaining of attacks of right upper quadrant pain since the age of 7 years. Past history revealed mild hydrocephalus in infancy and tonsillectomies at the ages of 7 and 18 years. The attacks of pain occurred every one to three weeks, lasted several hours, were accompanied by vomiting, and left him with a soreness in the upper abdomen that persisted for from twenty-four to thirty-six hours. The pain radiated to the right shoulder just as in biliary colic. There was never any jaundice. At the age of 21 years his gall bladder was removed at another institution. (It was impossible to get a description of the organ.) During the first postoperative week he had an attack of pain just like his previous ones. After discharge from the hospital the attacks recurred with the same frequency, intensity, and radiation. Between attacks he feels all right and can eat any kind of food. He has gone as long as five months without a seizure and feels best during the fall and early winter. In addition to the bouts of pain, he has, at irregular intervals, episodes of marked weakness, chills, pallor, and sweats. He also has frequent frontal headaches, cold sensations along both shins, numbness and cramps in both calves sometimes accompanied the episodes of weakness.

Physical examination revealed a thin, somewhat nervous, introspective individual. The head and neck were normal. The heart and lungs revealed no abnormality. The

blood pressure was 110/80. The abdomen revealed a well-healed right upper quadrant scar. There was no tenderness or rigidity. The extremities were normal. The blood Wassermann test was negative. Blood counts and urinalyses were normal. X-ray studies were not done since none was especially indicated. Chronic hypoglycemia was suspected because of the varied nervous symptoms. A glucose tolerance test done in April, 1938, revealed: fasting 65; one-half hour, 145; 1 hour, 100; 2 hours, 70; 3 hours, 70; 4 hours, 50. He was put on a low carbohydrate diet at once with feedings between meals. The attacks of pain stopped at once and he has had no further attacks up to the present time of writing, January, 1940. The episodes of weakness, chills, pallor, and sweats have likewise disappeared.

*Comment.*—The response to the change in diet in this patient was most dramatic in view of the twenty-nine-year history. The attacks stopped at once. It is very likely that the gall bladder removed was a normal one and the surgeon felt that its removal might relieve the patient of further pain simply because there would be no gall bladder present to contract. Since the localization and radiation of the pain after the operation were the same as before removal of the gall bladder, it is likely that the common duct, or the hepatic ducts, were being stimulated to strong contraction. That a correct diagnosis of chronic hypoglycemia should have been made in 1923 when the patient was operated upon is not to be expected since Harris published his first paper on the subject in 1924.

The patient's attacks began at the age of 7 years and occurred at intervals of one to three weeks. Between attacks he felt all right. If the bouts of pain were due to an inflammatory disease or stone, the course of the disease would have progressed in a few years to some stage requiring surgery. Pain due to biliary tract inflammation or stone does not manifest itself in this fashion over a long period of years. Now that the cause of the pain is definitely established, the syndrome could only have been caused by some labile mechanism that could come at intervals, cause much pain and discomfort for twenty-four to thirty-six hours, and then disappear. Such a reversible mechanism as a disturbance in blood sugar regulation fits in very well. While the patient had a chronic hypoglycemia, it may be said that the metabolic disturbance became aggravated periodically, at which time the hypoglycemia became more marked and brought on the bouts of pain. Since recovery from an attack was always spontaneous after twenty-four to thirty-six hours, such recovery may be attributed to the body's defense mechanisms capable of overcoming the hypoglycemia by mobilizing glycogen stores. Such mechanisms would be the adrenal-sympathetic system, the thyroid gland, and the anterior lobe of the pituitary. It is conceivable that these opposing hyperglycemic forces may respond beyond the point necessary to overcome the hypoglycemia and that their combined activity persists for several days or longer. The patient's diet with its high carbohydrate intake would then tend to increase the tolerance to glucose, depress the blood sugar levels again, and the cycle would be repeated.

CASE 4.—S. M., white female, 28 years of age, single, was first seen by me in December, 1938, complaining of attacks of epigastric and right lower quadrant pain and headaches of about seventeen years' duration. In recent years these had become almost daily occurrences. She had had the usual childhood diseases. Since the age of 11 years she had been subject to frequent attacks of abdominal pain, localized at times to the epigastrium and at times to the right lower quadrant. The pain in the epigastrium was cramplike, lasted a few minutes to one-half hour, was frequently accompanied by epigastric burning sensation and occasionally by nausea. She never vomited. The pain would come on one or two hours after a meal and disappear spontaneously. Sometimes she would get a sharp, severe, right lower quadrant pain lasting as long as two hours, accompanied by weakness, sweating, and dizziness. The headaches occurred almost daily and were described as "terrific." They were not localized to any specific part of the head.

The patient attended another clinic for several years because of her abdominal pain. Repeated physical examinations, various laboratory tests, and x-ray examinations of the gastrointestinal tract failed to yield clues as to the cause of her pain. An exploratory laparotomy was performed in September, 1934, and the appendix removed. The postoperative course was uneventful. The abdominal pain recurred shortly after she left the hospital. Pains and headaches continued during 1935, 1936, and 1937. In May, 1937, she spent two weeks at a leading neurologic clinic undergoing investigation for possible brain tumor. No evidence of tumor was obtained.

I first saw the patient in December, 1938. The history suggested chronic hypoglycemia as the most likely diagnosis. Examination revealed a moderately nervous, tense, worried individual. There were no abnormal physical signs. The abdomen was completely negative except for a well-healed scar. A glucose tolerance test revealed the flat type of curve: fasting 80; 1 hour, 85; 2 hours, 77; 3 hours, 80. She was put on a low carbohydrate diet. She was unable to take some food between meals because of the nature of her work. She was able to take some at bedtime. The abdominal pain stopped after one week. The headaches became milder and less frequent after two months but did not disappear completely until after four months. She became less nervous and jittery and volunteered that she "felt like a new person." A few times she went back to her former high carbohydrate diet and each time she had recurrence of pain and headache after seven to ten days. She lost eight pounds, going from 132 pounds to 124 pounds in the first two weeks on the diet. She then regained 9 pounds in the following four weeks and has remained at 133 pounds right along. At present, after thirteen months, she continues symptom free.

*Comment.*—The most dramatic feature in this case was the prompt cessation of pain. The headaches ceased after four months although they started to become less severe after two months. This same type of response was observed in Cases 1 and 2; i.e., the pain disappeared much sooner than did the headache.

Although the attacks of abdominal pain and headache are due to the fall in blood sugar, the ingestion of food usually affords relief from pain much sooner than relief from headache. In the case of pain the fall in blood sugar affects the vagal neurons which then stimulate smooth muscle to contract vigorously. The rise in blood sugar following food intake readily reverses this mechanism and pain disappears after several minutes or one-half hour. Pain due to simple hyperperistalsis will dis-

appear sooner than pain due to sustained tetanic contraction. Headache, on the other hand, often persists for hours in spite of recovery from hypoglycemia and suggests that the mechanism responsible for it is not so readily reversed. As mentioned previously, there is probably an escape of fluid through the capillary walls into the brain substance.

CASE 5.—C. S., white female, aged 23 years, single, was admitted to Morrisania Hospital on Sept. 22, 1937, complaining of severe headaches, dizziness, abdominal pain, loss of weight, and attacks of unconsciousness since 1930. She had had usual childhood diseases and an attack of pneumonia at 6 years of age.

In 1930 at the age of 16 years she began to have severe left-sided parietal headaches, which would last several hours, make her quit her work or whatever she was doing and go to bed. Weakness, dizziness, and nausea often accompanied these headaches. Vomiting frequently terminated them. At first the headaches occurred at weekly intervals. After a year they came on two to three times a week. She also had recurrent attacks of epigastric pain, tightness, or soreness, which were often relieved by eating.

The patient lived in a small Pennsylvania town. In 1932 she was admitted to the local general hospital for observation. A workup was negative and she was discharged with a diagnosis of migraine. In 1933 she was employed as secretary in a physician's office. An x-ray examination of the stomach and duodenum showed no abnormality. Because of the persistence of the abdominal pain, appendectomy was advised. This was done but she was not relieved. In 1934 she was admitted to another hospital in Pennsylvania where the only positive finding was a moderate hypertension of 150/100. In February, 1935, she spent three weeks at a leading neurologic clinic in Philadelphia. Repeated neurologic examinations were negative. Special examinations, such as x-rays of the skull, visual fields, and encephalograms, were negative. In 1936 she attended the out-patient department of a New York City hospital, where x-ray examinations were made of the stomach and duodenum and the biliary tract. These were negative. The blood pressure on two occasions was found to be 130/88 and 140/86. A fasting blood sugar was 102 mg. She was given a course of injections of calcium lactate for the migraine, but without relief. During the first six months of 1937 she had three attacks of unconsciousness without convulsions. These lasted about twenty minutes and recovery was spontaneous. She had lost 26 pounds from 1930 to 1937.

She was admitted to Morrisania Hospital on Sept. 22, 1937, and remained there until Nov. 22, 1937, undergoing a most thorough workup. Examination revealed an asthenic, worried, intelligent individual. There were few positive findings. The disks were poorly outlined but not elevated. The retinal veins were engorged, but no hemorrhages or exudates were seen. The blood pressure was 132/80. There was a small area of tenderness without rigidity on deep pressure just to the left of the umbilicus. The following special tests were done and reported as negative: visual fields, vestibular tests, basal metabolism, x-rays of the skull, encephalograms, blood and spinal fluid serologic tests, blood counts, and urinalyses. Three specimens of urine failed to reveal the presence of follicle stimulating hormone. Single blood sugar specimens were reported to be 75, 105, 100, and 90 mg. The patient had headaches about twice a week during her stay in the hospital. These were severe, lasted six to ten hours, and forced her to go to bed. On Oct. 17, 1937, the intern made the following note: "11:50 A.M.: Patient has excruciating headache. In view of previous report of low blood sugar (75 mg.) during episode of headache. 25 c.c. of 50 per cent glucose injected intravenously. Effect to be noted. 1:30 P.M.: Patient is now free of headache and feels fine. At 12:20 P.M., about 20 minutes after glucose was given patient states that her head became 'lighter.'

At 12:30 P.M. she was free of pain. This symptomatic relief warrants consideration of a hypoglycemic state as the cause of these headaches." On another occasion the patient was not relieved so readily by glucose. Glucose tolerance test Oct. 26, 1937, revealed: fasting 80; one-half hour, 85; 1 hour, 80; 2 hours, 80; 3 hours, 80, the "flat" type of curve. A second test Oct. 29, 1937, revealed: fasting 90; one-half hour, 100; 1 hour, 80; 2 hours, 65; 3 hours, 75; 4 hours, 90. The patient was discharged on Nov. 22, 1937, and returned to her home in Pennsylvania. She was told to stay on a low carbohydrate diet. I have been in touch with her by mail. The abdominal pain, tightness, and soreness have been much milder and she has been free of them for long intervals. The headaches have been just as frequent, although many have lasted for much shorter periods of time. She reports that her appetite is always poor and she is unable to take as much food as the diet calls for. She had no attacks of unconsciousness during 1938. Late in 1939 she had two such seizures.

*Comment.*—Just why this patient did not respond to the change in diet as did the other four patients is difficult to say. Her headaches were far more severe than those suffered by the others, suggesting that she had a more seriously deranged carbohydrate metabolism. My own experience suggests that patients who give the flat type of curve in the tolerance test respond less readily to the change in diet than do patients with other types of curves. The fact that the blood sugar values in the flat curve are often found to be in the low normal range, i.e., 80 to 90 mg., compared with the fall to marked hypoglycemia, 35 to 50 mg. as observed in other curves, suggests that there are certain unknown factors responsible for the variation in response to the ingestion of glucose. In general, the more severe the hypoglycemia, the better the response to therapy, since it is an easy matter to raise the blood sugar levels in such cases. It appears, then, that in patients with the flat type of curve even on a low carbohydrate diet the liberation of glucose from the liver is greatly inhibited. De Takats and Cuthbert<sup>21</sup> have shown that there is an increase in the storage and fixation of glycogen in the liver after suprarenal denervation and splanchnic section on normal dogs. These workers also suggested that clinically there may occur a block which inhibits the breakdown of liver glycogen. Such a block may conceivably occur in patients in whom the sympathetic nervous system is deficient or in whom the parasympathetic is preponderant.

Dorst<sup>22</sup> has successfully treated with small doses of insulin a group of patients with the flat type of curve. This response to insulin would tend to disprove that such fixation of liver glycogen is due to an excess of endogenous insulin.

#### DISCUSSION

While only five cases of chronic hypoglycemia are reported in this paper, the ideas and conclusions expressed are based on observations made on a larger number of patients with abdominal pain due to hypoglycemia. These five cases were selected from the group only because

they had undergone laparotomy. Chronic hypoglycemia is a common disorder masquerading as pseudoulcer, chronic appendicitis, abdominal migraine, abdominal angina, effort syndrome, neurocirculatory asthenia, larval hyperthyroidism, etc. The fact that the great majority of patients respond to a low carbohydrate diet suggests that the fundamental cause of the metabolic disturbance is the continued ingestion of a high carbohydrate diet which contains 200 Gm. or more of carbohydrate daily. The diet employed in treatment allows around 100 Gm. of carbohydrate daily. This amount may be increased gradually as long as the patient continues symptom free.

Patients with unrecognized hypoglycemia are often labeled neurotics because no evidence of organic disease is present to account for the abdominal and cerebral symptoms, and because such symptoms often disappear with change in environment, after a heart-to-heart talk with the physician, suggestive therapy, and placebos. Further, such symptoms may be aggravated by, or may recur following, psychic trauma, mental upsets, financial and domestic difficulties. It occurred to me that such unpleasant environmental factors could bring about visceral and mental symptoms by deranging the carbohydrate metabolism. Sudden bad news, for example, could bring on abdominal pain, or even syncope, by causing a sharp fall in the blood sugar. The following observations which I made on patients not included in the cases reported but included in the larger unoperated group illustrate the effect of unpleasant physical and psychic experiences on the blood sugar.

*Hypoglycemia and Syncope Following Venipuncture (Fig. 2).—*A white male, aged 50 years, reported to the clinic for a glucose tolerance test in the morning after an all-night fast. The patient fell unconscious about three minutes after the venipuncture, was unconscious for two minutes, and recovered spontaneously. The fasting blood sugar was 95 mg. On recovery from syncope, it was 65 mg. It is very likely that the blood sugar had fallen to even lower than 65 mg. and was on the rise when the second specimen was drawn since regain of consciousness must have depended on recovery from hypoglycemia. Such recovery may be attributed to the liberation of adrenalin. The pallor and cold sweat in syncope are evidence of such adrenal-sympathetic activity. I suggest that the syncope was due to the sudden fall in blood sugar precipitated by the unpleasant experience; namely, the venipuncture. Such a sharp fall in blood sugar may result from a cessation in the liver output of glucose mediated by a nervous or humoral mechanism.

*Hypoglycemia Following Sudden Bad News (Fig. 3).—*A white male, aged 17 years, with a long history of abdominal pain due to hypoglycemia, was suddenly informed that he was to be operated upon the next day. He was obviously upset, appeared pale, and described a feeling of faintness in the precordium and abdomen. He regained composure after several minutes concomitant with a rise in blood sugar. The

fall in blood sugar was not as great or as rapid as in the patient who fainted after venipuncture, but it was of sufficient magnitude to cause moderate visceral discomfort.

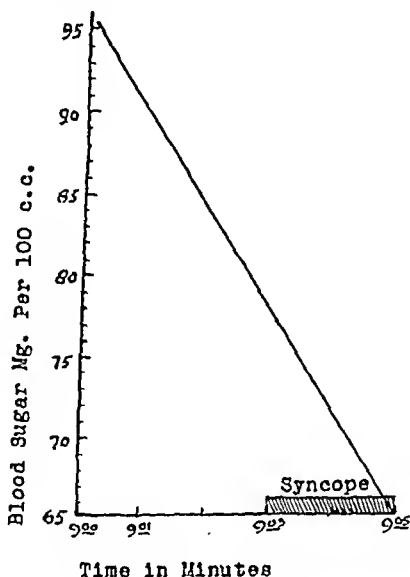


Fig. 2.—Syncope following venipuncture at start of a glucose tolerance test. At 9:00 A.M. fasting blood sugar was drawn. At 9:01 the patient was given 100 Gm. of glucose in 250 c.c. iced water. At 9:02 he appeared pale and nervous. At 9:03 he fell unconscious to the floor. At 9:05 he recovered spontaneously, at which time the second blood specimen was drawn.

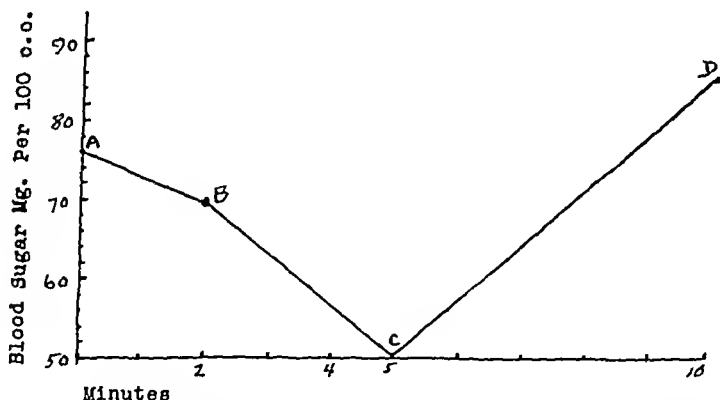


Fig. 3.—At A control blood specimen was drawn and subject was told that he was to be operated upon the next day. At B blood specimen was drawn and the patient said he had a "weak feeling" in the region of the heart and stomach. At C he felt worse, appeared anxious and pale. At D patient regained composure and said he felt better.

It has long been known that emotional disturbances may cause hyperglycemia and glycosuria. Such hyperglycemia has been regarded as a defense mechanism in that it increases the amount of glucose available for energy purposes during a period of stress. It is very likely that

immediately following a sudden unpleasant change in environment there is a transient hypoglycemia which is responsible for the unpleasant visceral and mental sensations, such as faintness, abdominal discomfort and pain, nervousness, tremors, pallor, tachycardia, and palpitation, which go to make up what we call fright and fear. Recovery from this phase and efforts made to protect the organism depend on a subsequent hyperglycemia. The individual who faints or who makes no attempt to defend himself probably has no such hyperglycemia.

Through a similar mechanism, chronic psychic trauma may cause chronic symptomatology by derangement of the mechanism controlling carbohydrate metabolism and blood sugar regulation. It is a matter of common knowledge that diabetes is often aggravated by worry or other unpleasant emotional states. This adverse effect is manifest by an increase in the hyperglycemia, signifying that the glucose is not being utilized and is accumulating in the blood. In severe cases the diabetes may become uncontrollable and lead to acidosis and coma. The final common effect, in both diabetics and nondiabetics, of such emotional states will be the same; namely, a decreased glucose and oxygen consumption. Abdominal pain, headache, and dizziness, occurring under such circumstances in both diabetics and nondiabetics, will be due to this final common effect. Thus may be explained the abdominal pain frequently encountered during diabetic acidosis; it is due to the reduced glucose utilization and disappears when such utilization is restored with insulin.

It is thus apparent that the mechanism governing carbohydrate metabolism and blood sugar regulation is a sensitive one and is especially influenced by the emotional state of the patient. Carbohydrate metabolism may thus be unfavorably influenced by a high carbohydrate intake and by psychic trauma. Since it is often difficult to remove the latter, much may be done by dietary management. If, then, a patient presents himself with symptoms obviously due to psychic trauma, he may be relieved of such symptoms by either removing the cause, i.e., the trauma, or by elevation and stabilization of blood sugar levels with a low carbohydrate diet. On such a diet the unfavorable effect on the blood sugar brought on by the psychic trauma is neutralized and symptoms are prevented. We have, therefore, a medium whereby unpleasant emotional states may give rise to a variety of functional symptoms. By depression of blood sugar levels such emotional states may reduce the amount of glucose available for cellular utilization and indirectly reduce the oxygen consumption in the organism. The function of every cell that utilizes glucose as a source of energy will therefore be affected. The severity of the functional disorder will depend on the magnitude of the derangement of the carbohydrate metabolism, and whether or not the changes in cellular function are reversible.

*The Relationship Between Fluctuations in Blood Sugar and the Hunger Mechanism.*—Normally, after a meal, the blood sugar rises to around 120 mg. in the first hour, 130 mg. in the second hour, 140 mg. in the third hour, and then falls to previous fasting levels, around 80 to 100 mg., during the fourth hour. The only symptom that should occur during the period of decline is the sensation of hunger. The fall in blood sugar stimulates the vagus which in turn causes an increase in gastric motility and tone. Cannon and Washburn<sup>23</sup> showed that "strong contraction of the muscle fibers of the wholly empty stomach, whereby its cavity disappears, makes a part of the sensation which we call hunger." Dickson and Wilson<sup>24</sup> injected insulin into human beings and noted that there was an increase in tone, depth, and rate of peristalsis of the stomach about an hour after the injection, when the blood sugar was around 70 mg. As was shown by Bulatao and Carlson<sup>7</sup> in dogs, and by La Barre and Destree<sup>9</sup> in human beings, gastric motility was replaced by atony when the blood sugar was depressed still further. This explains the loss of hunger and the sensation of epigastric hollowness and emptiness encountered in patients with chronic hypoglycemia where the blood sugar may be maintained for long periods at hypoglycemic levels. Further, in patients who give the flat type of curve in the tolerance test, as an additional cause for the lack of hunger, is the absence of adequate fluctuation in blood sugar levels necessary to stimulate the hunger mechanism.

A most common complaint in individuals after psychic trauma or during periods of worry is loss of hunger sensation. In the neurotic disorder, anorexia nervosa, the glucose tolerance is abnormal and the curves obtained are chiefly of the flat type. Return of hunger, gain in weight, and improvement in mental status, regardless of the therapeutic measures employed, are associated with an improvement in the carbohydrate metabolism. The following is from a recent paper by Ross.<sup>25</sup> He writes, "The conception of anorexia nervosa put forward is that . . . the physiological factor of impaired glucose tolerance with a slowly falling alimentary hyperglycemia leads to a failure of hunger and the impairment of one element of appetite—a normal gastric tonicity. . . . It seems clear, then, that there is a relationship, be it causal or coincident, between the gastric manifestations of hunger and a fall in blood sugar level, and it would be strange if it were merely coincident. If it is causal, then a reasonably rapid fall of alimentary hyperglycemia back to fasting level is necessary for the regular occurrence of hunger; and this fall we know is dependent on a reasonably good glucose tolerance."

One may state that the psychic trauma responsible for anorexia nervosa has disrupted the blood sugar regulatory mechanism which now brings in its wake loss of hunger and a variety of symptoms. Complete removal of the psychic trauma, if this is possible, usually cures the patient. One may say that its removal restores the regulatory mechanism

to its normal status. Where complete removal is impossible, other measures, such as psychotherapy, psychoanalysis, suggestive therapy, hypodermic injections of inert solutions, or time with its ability to make one forget, may cure the patient. These varied therapeutic measures apparently accomplish a final common effect; namely, a restoration to normal of the carbohydrate metabolism.

#### SUMMARY

Five patients with long histories of recurrent attacks of abdominal pain are reported. In four patients laparotomy failed to disclose organic cause for the pain. Appendectomy was performed in three patients and cholecystectomy in one. A herniorrhaphy was done in the fifth patient. These procedures afforded no relief. In addition to the pain all five patients had nervous manifestations of hypoglycemia which were not accorded their proper significance. Glucose tolerance tests revealed increased tolerance in all. Low carbohydrate diets afforded relief from pain and other nervous symptoms. Glucose tolerance tests should be done along with x-ray studies in cases of obscure abdominal pain.

The adverse effect of unpleasant emotional states on carbohydrate metabolism is discussed. It is suggested that such a derangement in carbohydrate metabolism may serve as a medium whereby psychic trauma may cause functional disorders.

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## ACUTE APPENDICITIS IN A SUBURBAN COMMUNITY

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FOR SEVERAL years the mortality figures of acute appendicitis have been of increasing interest to surgeons and public health officials. The importance of the subject is shown by a chart taken from the United States Bureau of Census for 1936, listing conditions which have been selected because of their surgical significance, omitting purely medical conditions.

Much has been done to correct unsatisfactory conditions, but the countrywide mortality in 1936 was 12.8 per 100,000, exactly the same as it was in 1917.<sup>1</sup>

As might be expected, the figures are worse in the rural states due to the "mechanics of isolation" (Krech<sup>3</sup>). Thus, in 1935 the rate in Idaho was 20, in Montana 20.2, in Utah 23.1, while in the same year in New York City the rate was 12.6 and in Philadelphia was 11.

Philadelphia has taken the lead in attempting to control this mortality. Under the chairmanship of J. O. Bower, a Commission on Appendicitis Mortality has worked in collaboration with the Board of Health, the state and county medical societies, the Board of Education, and the Association of Retail Druggists, with gratifying results. Recently, Bower has reported that over a nine-year period the mortality among patients admitted to twenty-eight Philadelphia hospitals has been reduced nearly 60 per cent.<sup>2</sup> Similar efforts throughout the country would mean a saving of 9,600 lives annually in the United States.

The efforts of the Philadelphia committee have been largely directed towards educating the public in the importance of abdominal pain lasting more than a few hours; the danger of cathartics; and the importance of calling in a physician.

Similar efforts have been made in New York City toward the reduction of mortality from contagious diseases, with the result that, while in 1920 there were 2,876 deaths from measles, whooping cough, scarlet fever, diphtheria, typhoid, and epidemic meningitis, in 1933 the deaths from these diseases had fallen to 629, a reduction of 78 per cent. Yet in the same year the deaths from appendicitis rose from 792 to 1,149, a 45 per cent increase.

In 1935 Krech<sup>3</sup> presented to the New York Academy of Medicine an exhaustive study of acute appendicitis in the years 1921 and 1931 in fourteen of the better New York hospitals. He found a mortality rate of approximately 7 per cent in both years, although there was improvement in earlier hospitalization and in a shorter time elapsing before the patient reached the operating room after admission. It was

interesting to note a marked increase in 1931 in the mortality in the older age groups, perhaps due to the ill effects of unemployment and economic stress.

There have been other similar studies from larger communities, all with much the same figures. Among the more recent of these may be mentioned that of Patterson,<sup>4</sup> reporting 1,211 cases of acute appendicitis from the University Hospital, Iowa City, Ia., from 1919 to 1934, with a 5.2 per cent mortality. In this series there was practically no change in successive five-year periods.

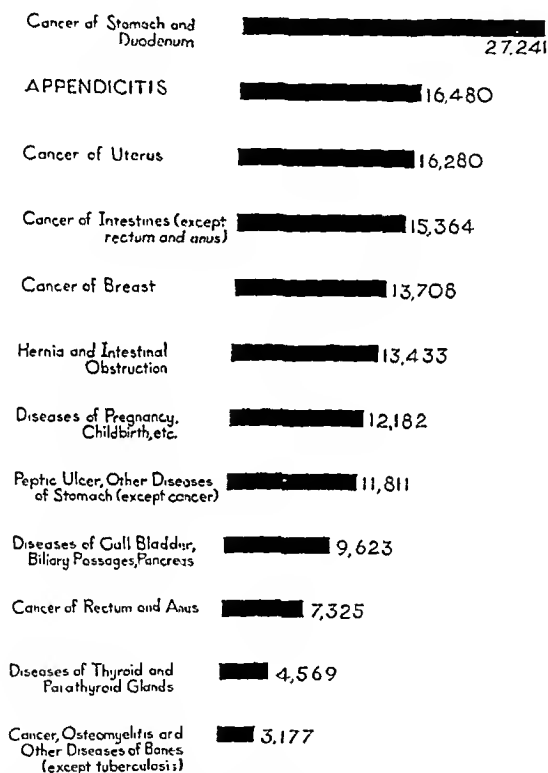


Fig. 1.—Deaths from certain causes in the United States, 1936. (From the U. S. Bureau of the Census, Vital Statistics Report, vol. 5, no. 41.)

Like other writers, Patterson emphasizes the increase in mortality in the later age groups, his series having a mortality of 3.6 per cent in the age group of 11 to 49 years; 16.44 per cent for those over 50 years of age. Hobler,<sup>5</sup> reporting from the Methodist Episcopal Hospital in Brooklyn, N. Y., cites 2,260 cases from 1924 to 1934, with a mortality percentage of 4.3. He quotes Black, who in 1932 reviewed reports from 150 hospitals, totaling 83,144 cases, with an average mortality of 5.5 per cent.

Baneroft,<sup>6</sup> reporting a series from the New York Hospital in 1920, and from the Fifth Avenue Hospital in 1935 to 1936, showed an essentially unchanged mortality rate of 4.3 and 4.2 per cent respectively.

Schullinger,<sup>7</sup> in a very thorough study of the Presbyterian Hospital (New York City) cases from 1916 to 1934, reported an average mortality rate of 5.08 per cent in a total of 2,653 cases, and quotes from various other hospital reports. He felt that there was a slight improvement over this period as a whole.

The most recent reports come from Ravdin and co-workers,<sup>8</sup> who report from Ravdin's service in the Hospital of the University of Pennsylvania. He divides his cases into those previous to and those after 1936, coincident with a change to the consistent use of sulfanilamide in severe cases, especially if there is any peritoneal involvement. In the earlier group he had 8 deaths in 552 cases, a 1.4 per cent mortality, while in the later series there was 1 death in 357 cases, a rate of 0.4 per cent. These figures are the more striking in that acute catarrhal appendicitis is not included.

Arnheim and Neuhof<sup>9</sup> report from Neuhof's service at Mt. Sinai Hospital 212 cases operated upon between 1931 and 1939 with 4 deaths (1.9 per cent).

This report is noteworthy for the absence of a fatal result in 40 consecutive cases of appendicitis with abscess, the average in most other reports running from 5 to 10 per cent. They attribute their good results to a meticulous operating technique, their pre- and postoperative care not differing markedly from that of other authors.

Gile and Bowler<sup>10</sup> reported in 1934 their figures from Hanover, N. H., for a six-year period. Their figures were particularly interesting because they were able to present two groups, one made up of Dartmouth College students living under fairly close control, the other made up of patients within the 75-mile radius served by the hospital. Both groups were cared for in the same hospital by the same surgeons. In the college group there were 110 cases with no deaths. Of these only 1 had gone on to abscess, 1 to diffuse peritonitis. In the general group there were 791 with 17 deaths, a mortality of 2.15 per cent. In this group there were 29 abscesses, 21 cases of diffuse peritonitis. The total figures are 901 with 17 deaths, 1.89 per cent.

Aside from the question of preoperative preparation, operative technique and aftercare, the problem of appendix mortality is chiefly one of education, of the patient or his family in the importance of early medical care and the avoidance of self-medication, and of the physician in early diagnosis and early reference to the hospital.

In discussing the possibilities of improvement, the general tendency is to emphasize early operation and the danger of catharsis. Schullinger perhaps presents the best summary of the factors in the mortality as follows: (1) fears and superstitions of hospitals and operations; (2) cathartics to children for abdominal cramps; (3) purgatives and laxatives prescribed by pharmacists; (4) misinterpretation of ab-

dominal signs and symptoms; (5) medical treatment (morphine, rest, icebag) by local physician; (6) the occasional operator.

While early operation is universally emphasized, it is becoming more clearly recognized that delay of a few hours to correct a depleted fluid balance by infusion is of more value in appropriate cases. Adopting this principle, Beekman<sup>11</sup> has been able to report 136 cases from the children's surgical service of Bellevue Hospital with no deaths.

It is in the late case, with signs of peritonitis not localizing, that the greatest difference of opinion exists. Both immediate operation or Ochsner treatment have their advocates and we believe that Patterson<sup>4</sup> is correct when he says that treatment should be individualized and suit the patient rather than be dogmatic.

It seems that the advocates of Ochsner treatment should emphasize that it is a method that should be carried on in the hospital and under the supervision of the surgeon; otherwise the physician will naturally come to believe that it is a method that can safely be carried out in the home and without surgical aid, a belief that will quickly be reflected in a rising mortality rate.

With the problem in part at least one of public education, and because relatively few studies have been published from smaller communities other than those of individual clinics and surgeons, it has seemed worth while to study the disease as it has occurred in Greenwich, Conn., a suburban community town of 40,000 with almost no factories, a well-trained medical group and a population whose "health sense" has twice won the annual health conservation certificate awarded by the United States Chamber of Commerce.

During the period from June 1, 1933, to Dec. 31, 1939, 525 cases of acute appendicitis have been operated upon at the Greenwich Hospital. Interval operations and appendicees removed in the course of operation for other primary diseases have not been included. No case has been included unless the pathologic report substantiated the diagnosis, with the exception of those in which an abscess was drained but the appendix not removed.

TABLE I  
AGE GROUPS AND RELATION TO MORTALITY

				DEATHS
To 10 yr.	61 (11.6%)	} 449 cases (mortality 0.2%)		1
10-20 yr.	192 (36.5%)			
20-30 yr.	130 (24.7%)			
30-40 yr.	66 (12.5%)			
40-50 yr.	40 (7.6%)	} 75 cases (mortality 8.0%)		2
50-60 yr.	20 (3.8%)			
60-70 yr.	14 (2.6%)			
70-80 yr.	1 (0.19%)			
Not noted	1			

This emphasizes, as do all published reports, that acute appendicitis is a disease of young adult life and that the mortality is greater in the later decades. Sprague<sup>12</sup> reports a mortality rate of 1.5 per cent in 81.5 per cent of 1,463 cases from the Newark City Hospital between the ages of 10 and 40 years, but a 13.9 per cent mortality in the group from 40 to 80 years of age.

TABLE II  
DURATION OF ATTACK AND RELATION TO MORTALITY

				DEATHS
To 12 hr.	175 (33.5%)	} 465 (mortality 0.8%)		1
12-24 hr.	194 (36.9%)			
24-48 hr.	96 (18.2%)			
48-72 hr.	22 (4.4%)	} 54 (mortality 11.0%)		3
72-	32 (6.0%)			2
Not noted	6 (1.2%)			1

These figures are in line with others and emphasize the remark of Ashurst:<sup>13</sup> "There is no problem in acute appendicitis—the problems of appendicitis are the problems of its complications."

*History.*—One hundred and fifty-four patients had had previous attacks.

The present attack as described in the records was typical in 505, atypical in 16, and not noted in 4. The first symptom was pain in 507 cases, nausea and vomiting in 9, diarrhea in 9.

TABLE III  
CATHARSIS

Taken by 181 patients			
No record	97	Ordered by family	52
None taken	247	Ordered by self	84
Oil	30	Ordered by physician	10
Salts	52	Ordered by druggist	2
Other	56	No note	33
Enema	79		

Catharsis is usually noted as one of the causes of increased mortality, but its true importance is not yet determined. Catharsis is the one detail which is most likely to be omitted in the intern's history. Thus, Kreeh found no mention of catharsis in 69 per cent of the 1921 charts,

TABLE IV  
RELATION OF CATHARTICS TO PREOPERATIVE DELAY

ENTIRE SERIES (525)		PATIENTS TAKING CATHARTICS (181)	
To 12 hr.	175 (33.5%)	39 (21.5%)	} 83.8%
12-24 hr.	194 (36.9%)	75 (41.4%)	
24-48 hr.	96 (18.2%)	38 (20.9%)	
48-72 hr.	22 (4.4%)	7 (3.8%)	} 22 (12.1%)
72- hr.	32 (6.0%)	22 (12.1%)	
Not noted	6 (1.2%)		

63 per cent of the 1931, while information was incomplete in 20 and 16 per cent, respectively.

While our figures represent a relatively small total, they are presented for what they are worth, and in part because we were surprised at the apparently slight effect of catharsis on delay in operation and on the extent of appendiceal involvement.

It may be that Nature protects the patient from the effects of unwise catharsis by rejecting it.

On the other hand, Bower<sup>14</sup> in reporting from 1928 to 1930 from Philadelphia makes the statement that when: no cathartic was given in the acute attack, 1 in 80 died; one cathartic was given in the acute attack, 1 in 13 died; two or more cathartics were given in the acute attack, 1 in 7 died.

It is our impression that cathartics may be more important as a cause of delay than in the actual local damage that they cause.

TABLE V  
RELATION OF CATHARSIS TO PATHOLOGIC STATE OF APPENDIX

ENTIRE SERIES (525)		PATIENTS TAKING CATHARSIS (181)	
Without peritonitis			
Acute catarrhal	70 (13.3%)	21 (11.6%)	77.8%
Suppurative	247 (47.0%)	72 (39.7%)	
Gangrenous	79 (15.0%)	48 (26.5%)	
Abscess	37 (7.0%)	12 (6.0%)	
Local peritonitis			
Suppurative and gangrenous	56 (10.6%)	15 (8.2%)	
Diffuse peritonitis			
Suppurative and gangrenous	29 (5.5%)	10 (5.5%)	
Not noted	7 (1.3%)	3 (1.6%)	

*Diagnosis.*—This was correct in 506 cases. In 12 the preoperative diagnosis could not be determined from the chart. The incorrect diagnoses were: perforated ulcer, 3; acute cholecystitis, 1; acute pancreatitis, 1; ovarian cyst with twisted pedicle, 1; abscess of abdominal wall, 1.

TABLE VI

INCISION		DRAINAGE	
No record	40	Peritoneal cavity	122
McBurney	347	Abdominal wall	20
Split rectus	42	Abscess, appendix not removed	3
Retracted rectus	94		
Midline	1		
Pfannenstiel	1		

We prefer the McBurney incision unless the diagnosis is questionable, feeling that it gives adequate exposure with minimum risk of peritoneal contamination and that drainage through this incision, if necessary, is satisfactory and least likely to be followed by hernia.

Drainage follows the usual rules and is usually established by a soft cigarette drain.

*Pathology.*—As one would expect, in view of the large number of early operations, the changes in 75 per cent of the cases were confined to the appendix.

The differentiation between local and diffuse peritonitis is difficult to be sure of, the interpretations of the individual surgeons probably varying considerably. Where the diagnosis as written did not check with the operative description, we have classified the case according to the latter.

TABLE VII

ANESTHESIA		PRELIMINARY MEDICATION	
Avertin base followed by G-O-E	431	Morphine and atropine	240
G-O-E	86	Atropine	210
Spinal	1	Morphine	19
Drop ether	5	Codeine	2
No record	2	Nothing	52
		No record	2

Obviously we are well satisfied with avertin as a basic anesthetic. We have not found the difficulties and danger in its use reported by Beecher<sup>15</sup> from the Massachusetts General Hospital where its use has been discontinued. In fairness it should be stated that we have an adequate and well-trained anesthetic and nursing staff, which we believe to be important when this anesthetic is used. The senior author, for instance, finds it a much less practical anesthetic on his service at Bellevue Hospital, where it is more difficult to give special attention to a patient when coming out of anesthesia.

The amount of preliminary medication has been somewhat of a surprise. While we have had no difficulties following the use of morphine and avertin, we feel that morphine as a preliminary is probably bad practice and should be abandoned as routine. This opinion is based on the emphatic statements of many of the more experienced anesthesiologists.

TABLE VIII\*

## POSTOPERATIVE COMPLICATIONS (525 CASES)

<i>Wound</i>	
Deep infection	16
Hematoma	7
Disruption	1
Secondary pelvic abscess	1
<i>Pulmonary</i>	
Pneumonia	7
Embolus	3
Bronchitis	2
<i>Gastrointestinal</i>	
Fistula	2

\*Figures of superficial infections, stitch abscesses, etc., are too incomplete to be of any value and are omitted.

*Mortality.*—There have been 7 deaths in this series, 1.3 per cent. As shown in Tables 1 and 2, deaths occur chiefly in the older age groups and in the late cases.

There were no deaths in the 396 cases in which the disease was limited to the appendix nor in the 37 cases of abscess.

One patient with local peritonitis (pelvic) died, a mortality rate in this group of 1.8 per cent.

Of 29 patients described as having diffuse peritonitis, 6 died (20.6 per cent).

Four of these 7 had been sick less than forty-eight hours. One was a patient who at operation had a *B. coli* pelvic peritonitis. She showed no resistance, dying eight days following operation with the signs of a spreading peritonitis.

The 6 who had diffuse peritonitis at operation were aged 36, 44, 48, 59, 66, and 68 years. They had been sick for 22, 30, 36, 36, 56, and 96 hours before operation. Three had had saline cathartics; two, irrigations before admission. There was no note as to catharsis on the remaining charts.

At operation all had gross leakage from ruptured appendices. *B. coli* were reported in all cultures.

Aside from the possible effect of catharsis, vigorous treatment by a physiotherapist may have been a factor in the rupture of one of these appendices.

In another case pain developed a few hours after eating clams which had been dug in a prohibited area, and this together with atypical signs led to delay in operating until peritonitis was well established.

There were two errors in diagnosis. In one case a previous history of ulcer and fulminating signs led to a diagnosis of perforated ulcer, an error which had no influence on the ultimate result. In the other what was thought to be a gangrenous gall bladder was removed and only after its removal was a gangrenous appendix recognized. In this case an unnecessary procedure prolonged the operation and probably was a factor in the patient's death.

#### SUMMARY

A partial review of recent literature covering the mortality figures of acute appendicitis is presented. The figures from a suburban community of 40,000 population, with a high average intelligence and "health sense," as well as a well-educated medical group, are discussed.

Even in a community of this sort, over 10 per cent of all cases were operated upon after a delay of over forty-eight hours. It is in the education of the public and the medical profession toward the further diminution of this figure that lies our best hope of further cutting down the mortality.

The mortality from acute appendicitis in this community over a seven-year period is 1.3 per cent.

Catharsis does not seem to be an important factor in the mortality rate in this series.

The use of sulfanilamide, especially in cases with peritoneal involvement, offers hope of improvement.

Study of the fatal cases emphasizes that overwhelming peritonitis may be established early and the importance of early recognition of the case with atypical symptoms and signs.

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## LIVER INJURIES WITH A CASE REPORT OF REPEATED HEMORRHAGES THROUGH THE BILIARY DUCTS

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THE symptoms of the usual liver injury include pain that may be severe and localized over an area in the liver or in the region of the blow, such as would be found in a lateral chest contusion. This type of injury may cause widespread pain similar to pleuritis.<sup>1</sup> Localized pain may be absent, but a liver injury should be kept in mind if there has been a blow or contusion anywhere near the region of the liver. Rigidity, shock, signs of internal hemorrhage or bile irritation of the peritoneum indicate an emergency, but these findings are often not pronounced enough to warrant opening the abdomen at once. Repeated blood counts will aid in differentiating hemorrhagic from traumatic shock. The apparently mild upper abdominal injury must be watched closely. Quick recovery from the immediate shock may be followed by delayed massive hemorrhage.

The right lobe, due to its anatomical position, is the most frequently affected. Any area may be involved and deep wounds by contrecoup may occur. Deep wounds may not show any external evidence of capsular tear and, as in the case to be presented, may bleed profusely through the bile ducts. Multiple tears and deep hematomas that are often followed by abscess formation are found at operation or autopsy.

Hematomas are aspirated and those that later go on to abscess formation are drained in the usual manner, but the technique of peritonization of the area to be drained as advised by Robertson<sup>2</sup> is probably the safest procedure.

A liver wound should be loosely packed because tight packing may cause necrosis. The gauze is allowed to remain in place for one week. In Krieg's forty-one cases that were treated by packing, the gauze was not inserted into the wound with enough pressure to control the bleeding and frequently it was merely placed against the wound. When large amounts of gauze were used there developed symptoms of obstruction.<sup>3</sup> Drainage is necessary because collections of blood, bile, or pus may occur. Closure of the wound by mattress sutures is a method that is preferred by many surgeons and, if this procedure is followed, drainage should be inserted into the depth of the wound in order to prevent the formation of an intrahepatic hematoma and to take care of the bile leakage from torn biliary ducts.

CASE REPORT.—(No. 21464, American Hospital for Diseases of the Stomach.) This was an unusual case of injury to the liver without rupture of the capsule and

intra-peritoneal bleeding but followed by repeated massive hemorrhages through the biliary ducts. The clinical picture and surgical treatment were therefore quite different from those just described.

A truck tire rim blew off, striking the anterolateral chest wall, upper abdomen, and face. The man was admitted to another hospital on June 6, 1933, where he was given immediate treatment for shock, fractured seventh and eighth ribs, and fractured nose. The injury to the thoracic cage masked the intraabdominal injury so that it was not recognized at this time in spite of hematemesis on two occasions and tarry stools that were noticed by the patient. After seven weeks of hospitalization he was discharged and returned to work nine weeks after the date of injury. Two weeks later while at work he felt a sudden sense of suffocation with severe pain in the upper abdomen but most marked in the gall bladder area. He vomited a large amount of blood and there was gross blood in the stool.

When admitted to our service on Sept. 17, 1933, he stated that he had vomited a large amount of blood that morning and gross evidence of blood was found in the stool.

The patient was a very powerful man and the general physical condition was surprisingly good in spite of all the bleeding that had reduced the red cells to 2,790,000 and the hemoglobin to 47 per cent.

All physical findings were negative but no gastrointestinal x-rays were attempted due to the continued bleeding. Nothing was given by mouth for three weeks and by the use of blood transfusions and intravenous glucose he improved to the extent that the red cell count was 4,190,000 and hemoglobin 70 per cent. During this time, however, he vomited on three occasions a very thick black material that on examination proved to be a mixture of blood and bile. The stool finally was negative and after three weeks of withholding fluids by mouth, a liquid diet was allowed. The stool only remained negative for occult blood for two days and then traces appeared again. However, for psychological reasons an increase in diet was allowed and no increase in the bleeding occurred. For the same reason the patient was allowed to go home two months after admission, still showing a trace of occult blood in the stool, but was to return for a complete gastrointestinal x-ray.

He was readmitted to the hospital three weeks later and plainly showed the effects of a severe hemorrhage the night before. During the three weeks at home he had several attacks, consisting of a sense of tightness in the liver area and severe colicky pain followed by nausea and vomiting of the same thick black material that had been examined in the hospital. He also passed this same type of material by bowel.

Five days later the blood transfusions and intravenous glucose injections had caused sufficient improvement to warrant an x-ray examination of the stomach and duodenum. A large defect in the pyloric end of the stomach was demonstrated, but the roentgenologist was unable to state whether this was due to adhesions or ulcer.

After two more days of blood transfusions and intravenous glucose injections an upper right rectus incision revealed a mass of adhesions over the gall bladder and duodenal areas. No ulcer was demonstrable, but in view of the large amount of hematemesis it was deemed advisable to open the duodenum. The usual Heineke-Mikulicz incision was made. No definite ulcerated areas were found, but several small congested areas in the mucosa were touched with the cautery and the incision was closed transversely. This did not explain the bleeding and, on releasing the dense adhesions, the gall bladder was found to be very dark in color, to be enlarged, and to contain a smooth hard mass the size of an egg. The gall bladder was removed and the bile ducts were explored through the patulous cystic duct. Some very dark material of the same type that he had vomited was found, but there was no

evidence of tear of the ducts or liver. The large mass in the gall bladder proved to be inspissated blood and bile.

He made an uneventful postoperative recovery and was discharged on the sixteenth day. The stool was negative for occult blood.

One week later he had another attack of colicky pain in the subhepatic area lasting one hour and vomited a small amount of the very dark material that had been observed on previous occasions. A large amount of green black fluid was passed by bowel. There followed a number of these short attacks at intervals of a few days. During the last attack a branching clot that appeared to be a cast of the hepatic ducts was vomited. This proved on examination to be inspissated blood and bile. Since then he has been entirely free of all the former symptoms and at present is in excellent health.

It is very evident that the operative procedure did not contribute to the final cure, but it is interesting to note that this case was in all probability a cavity and hematoma deep in the substance of the liver that continued to necrose and bleed through a large biliary duct until healing finally occurred. There is no other explanation that we can give for the continued bleeding through the biliary channels.

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## THE ORAL ADMINISTRATION OF SYNTHETIC VITAMIN K (2-METHYL-1, 4-NAPHTHOQUINONE)

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SINCE the discovery of the relationship of hemorrhagic tendencies to vitamin K deficiency in 1929<sup>1</sup> and later in 1935<sup>2</sup> by Dam, there have been many reports corroborating his results and presenting further observations upon the source, extraction, assay, and clinical application of this vitamin. Some of the leaders in this experimental work have been referred to in a recent report by Doisy and his associates,<sup>3</sup> who have been responsible for the synthesis of vitamin K in their laboratory. They found that the synthetic compound was 2-methyl-1, 4-naphthoquinone. To support this contention, Almquist and Klose<sup>4</sup> and Fieser,<sup>5</sup> independently following different analytical procedures, arrived at the same structural formula. This compound was an oil-soluble active substance whose action was thought to be either through the phenol or quinone radicals. Since the substance could not be used parenterally except in a large volume of solvent, experiments were conducted to discover an active compound with greater solubility, and such a compound was found by Doisy and co-workers<sup>6</sup> to be 4-amino-2-methyl-1-naphthol hydrochloride.

Clinical application of vitamin K has been discussed and reviewed by Rhoads,<sup>8</sup> Snell,<sup>9</sup> Stewart and Rourke,<sup>11</sup> and others. Therefore, reference is made to their reports of original investigations regarding vitamin K and the natural substances rich in this vitamin. Before the synthesis of an active compound, the prime sources were alfalfa and putrified fish meal. Green leaves, vegetables, dried chestnuts, spinach, peas, and egg yolks also contained the active substance.

Vitamin K was intimately associated with the plasma prothrombin which was involved in the mechanism of the clotting of blood. Experimentally, a prolongation of the prothrombin time was produced in a chick by withdrawal of the vitamin in the diet. This could not be produced in other common laboratory animals. Hawkins and Brinkhous<sup>12</sup> produced a prothrombin deficiency in a dog with a biliary fistula, but it took several months to develop. Smith, Warner, and

Brinkhons<sup>13</sup> produced a marked hypoprothrombinemia in twelve hours by chloroform anesthesia, and a similar condition by administering phosphorus and carbon tetrachloride. These observations indicated that liver damage was responsible for the reduction of plasma prothrombin. This finding was supported by Warner,<sup>14</sup> who produced a marked prothrombin deficiency by partial hepatectomy. In six dogs Andrus and his associates<sup>15</sup> performed complete hepatectomies. They found a continuous decided fall in prothrombin concentration after hepatectomies and held this as evidence that the liver under normal conditions was responsible for the formation of prothrombin. As further proof, Andrus and associates instilled vitamin K into the duodenum and failed to alter the typical decreasing curve of the plasma prothrombin fall after hepatectomies. These experiments seemed to indicate that the liver was the chief, if not the only, source of prothrombin.

Clinically, liver damage might take place in various diseases, and thus hypoprothrombinemia might occur and predispose the patient to hemorrhagic tendencies. Any obstruction to the extrabiliary passages might secondarily cause damage to the liver. Primary liver disease through infections, neoplasms, metabolic or other factors might affect the parenchyma of the liver to such an extent as to produce a lowered plasma prothrombin level. Thus, if the "factory" were not functioning properly, one might expect that any efforts made to maintain a normal prothrombin level through synthesis by the liver would be futile.

Through any of the preceding factors an individual might develop a deficiency in bile salts because there was inadequate manufacture by the liver or because there was a "block" to the outlet of bile salts into the intestinal tract. Since vitamin K is a fat-soluble substance, its absorption depends upon the presence of bile salts in the intestinal tract. In addition, there might be insufficient absorption from the gastrointestinal tract, as in intestinal obstruction or ulcerative colitis. If there is obstruction to the flow of bile from the liver, there is presumably an inhibition of production of bile salts by the liver. If this obstruction is liberated, as through surgical intervention, a sudden release of stagnant bile occurs. Walters and others<sup>16</sup> have analyzed bile in such cases and found that the total bile-acids secretion might be definitely lowered. This accounts then for the inability of the body to utilize fully vitamin K in obstructive jaundice without the addition of normal bile salts even after the obstruction has been released. This phenomenon, however, is largely dependent on the presence of a damaged liver.

The prothrombin determinations in our series were done by the method of Smith\* and associates<sup>10</sup> because their "bedside" test had such practicability. In a comparison between the Smith and the Quick tests we found that the variation was slight with the exception of extremely low levels where the Quick test was more sensitive. For clinical use the percentage of error was within practical range. The values obtained were recorded in the percentage of normal; that is, the percentage of the prothrombin clotting activity of a normal individual. Determinations were done daily in most instances. Coagulation times by the capillary tube method were done in some of the patients, but no delay was noted except in two or three instances when the prothrombin clotting time was markedly prolonged.

This paper deals only with oral administration of vitamin K.† Several patients have been given a soluble vitamin K for parenteral use, but at present our series is too small to include in this report. However, the synthetic vitamin K for intravenous administration is active and promises to be about as effective as the insoluble type.

Seventy-five patients who had biliary tract surgery, or who were suspected of having a prolonged prothrombin time, were tested. Determinations were made daily; the prothrombin percentage recorded was the lowest reading obtained in each case. Eighteen patients treated were jaundiced (Table I). The prothrombin clotting activity reached normal levels in each instance. Rhoads and Fliegelman<sup>16</sup> and Macfie with his associates<sup>17</sup> have recently reported a good response with the synthetic vitamin in jaundiced patients. It is seen in Table I that there is little correlation between the degree of jaundice, or its duration, and the hypoprothrombinemia. Five patients (Table II) with a reduced prothrombin clotting activity, but not jaundiced, were also treated. The percentage of activity returned to normal in all except one case, a patient in terminal condition resulting from a carcinoma of the rectum.

\*Method of plasma prothrombin determination:

*Source of Thromboplastin.*—Rabbit brains or lungs are macerated in a mortar. Salt solution, 0.9 per cent, is then added. The material is allowed to stand in the icebox for three hours. The supernatant fluid is decanted and strained through gauze. Usually the solution is centrifuged. The thromboplastin, which is present in the filtrate, is kept in the icebox. It is best to warm the sample of thromboplastin to room temperature before using. The activity of the thromboplastin decreases daily; thus a normal prothrombin time for the sample of thromboplastin used must be made daily.

*Method of Prothrombin Determination.*—A stop watch is used for accuracy in timing the clotting time. One-tenth cubic centimeter thromboplastin is placed into a small serologic tube. To this is added 0.7 c.c. of blood drawn quickly and atraumatically. The time is recorded in seconds from the time the blood contacts the thromboplastin to the time the clot appears in the tube. The tube is slowly inverted until clotting occurs. A normal patient is tested and checked several times to get the correct normal prothrombin time.

Normal plasma prothrombin time in seconds

Patient's plasma prothrombin time in seconds  $\div$  normal clotting activity = percentage of normal clotting activity.

A prolonged prothrombin time in seconds will give a low percentage of clotting activity.

*Bleeding Levels.*—Bleeding may occur at any level below 70 per cent; however, it is relatively uncommon until the level has approached 50 per cent.

†The vitamin K and bile salts used in this report were kindly furnished by E. I. Lilly and Co., Indianapolis, and Parke, Davis and Co., Detroit.

TABLE I

JAUNDICED PATIENTS WITH REDUCED PROTHROMBIN CLOTTING ACTIVITY WHO RECEIVED VITAMIN K

CASE	DIAGNOSIS	JAUNDICE		INITIAL PRO- THROMBIN	AFTER VITAMIN K
		DURATION	DEGREE*		
1. A. B.	Carcinoma of pancreas	2 mo.	4	64%	100%
2. P. A.	Carcinoma of pancreas	1 mo.	4	75%	100%
3. S. V.	Common duct stone	6 wk.	3	37%	100%
4. P. L.	Carcinoma of pancreas	3 mo.	3	48%	100%
5. M. Me.	Carcinoma of pancreas	3 wk.	3	71%	100%
6. P. V.	Common duct stone	4 wk.	2	64%	100%
7. H. M.	Common duct stone	3 wk.	2	64%	91%
8. M. E.	Acute cholecystitis	10 days	2	67%	100%
9. J. P.	Cirrhosis of liver	1 mo.	2	69%	100%
10. H. M.	Acute cholecystitis	1 wk.	2	70%	96%
11. L. T.	Common duct stone	6 wk.	2	76%	100%
12. T. F.	Carcinoma of pancreas	6 wk.	2	76%	100%
13. M. M.	Cirrhosis of liver	2 mo.	2	77%	100%
14. F. G.	Cirrhosis of liver	1 mo.	2	79%	100%
15. M. R.	Common duct stone	4 wk.	2	79%	100%
16. J. A.	Common duct stone	2 wk.	1	54%	100%
17. M. H.	Common duct stone	2 wk.	1	62%	94%
18. D. W.	Cirrhosis of liver	3 wk.	1	74%	91%

\*Degree of jaundice: 1, slight; 2, moderate; 3, severe; 4, very severe.

The initial dose arrived at after our experimentation was 6 mg. of vitamin K and 2 Gm. of bile salts. As a routine, 0.33 Gm. (5 gr. capsule) of bile salts was given with each milligram of vitamin K. A daily dose of 2 to 6 mg. maintains a normal prothrombin level in most patients. The maintenance dose was determined and must be checked by daily prothrombin determinations. Our observations seemed to indicate that all low prothrombin levels can be returned to normal with an initial dose of 6 mg. and can be held with a maintenance dose of 6 mg. daily. In many patients the prothrombin time can be maintained at a normal level on a much smaller dosage.

TABLE II

NONJAUNDICED PATIENTS WITH REDUCED PROTHROMBIN CLOTTING ACTIVITY WHO RECEIVED VITAMIN K

CASE	DIAGNOSIS	INITIAL PROTHROMBIN	AFTER VITAMIN K
1. A. K.	Biliary fistula	57%	100%
2. O. P.	Intestinal obstruction	68%	100%
3. S. K.	Subphrenic abscess	67%	100%
4. C. A.	Carcinoma of rectum	69%	74%
5. E. C.	Nephritis	69% (bleeding)	98%

The following case illustrates the effect of the therapy:

Case M. R. (Fig. 1) presented a moderate degree of jaundice of four weeks' duration due to a common duct stone. Preoperatively, the prothrombin activity was 61 per cent. This patient was given 1 mg. of vitamin K three times daily, with 0.33 Gm. of bile salts to each milligram. After one dose the level in twenty-four hours was 74 per cent. In forty-eight hours after three doses the level reached 91 per cent. Such

a gradual rise in the plasma prothrombin was obtained with small doses. The level dropped to 75 per cent in twenty-four hours. Then, an initial 6 mg. dose of vitamin K and 2 Gm. of bile salts were given. A rise to 95 per cent was then attained in one-half hour. Other patients responded similarly to these doses. There is no objection to the use of small doses of the compound when preparing a patient for surgery; however, if an immediate effect is sought, an initial large dose is recommended.

Case M.R. Common duct stone with jaundice.

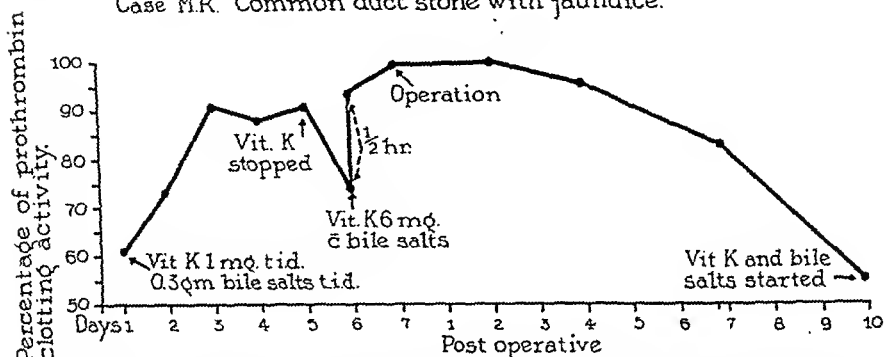


Fig. 1.—On a dosage of 1 mg. of vitamin K t.i.d. the prothrombin activity gradually rose to normal, then dropped as soon as the treatment was discontinued. On a single dose of 6 mg. the prothrombin activity rose sharply to normal in one-half hour. A choledochostomy was performed on the following day. Treatment was again discontinued. A gradual reduction in prothrombin activity recurred, reaching a low level on the tenth day.

Vitamin K must be given with bile salts when the latter are not secreted into the intestinal tract. We found that in the absence of bile salts the response was negligible. This was illustrated by the case of A. K. (Fig. 2); the patient gave a good response to an initial dose of 6 mg. of vitamin K with bile salts, rising from a 57 per cent level to 100 per cent. However, after the prothrombin time had dropped in twenty-four hours to 47 per cent, 6 mg. of the vitamin were given without bile salts, but there was no response. Then 1 mg. of the compound was given with 0.33 Gm. of bile salts, three times daily. After one dose, the level was 63 per cent. After four doses, the level was 100 per cent. Another patient, O. P. (Fig. 3), was treated for acute intestinal obstruction by Wangensteen gastric siphonage for seven days. A vitamin K deficiency was present due to starvation. We assumed that bile salts were secreted into the intestinal tract. Three milligrams of vitamin K were given without bile salts. The duodenal tube was clamped off for two hours. The level rose from 79 to 91 per cent in twenty-four hours. The next day it dropped to 70 per cent. Six milligrams of vitamin K, without bile salts, were given and in one-half hour the level was 90 per cent. In twenty-four hours it was again 90 per cent, and in forty-eight hours it was 100 per cent. Thus, one is guided by the etiologic factor of the vitamin K deficiency as to whether or not bile salts should be given in conjunction with vitamin K.

The response to the synthetic vitamin K is apparently immediate. We found that, when an adequate dose was given, a rise in the prothrombin level was obtained within one hour. Five patients were observed to determine the rapidity of action of the compound. In the

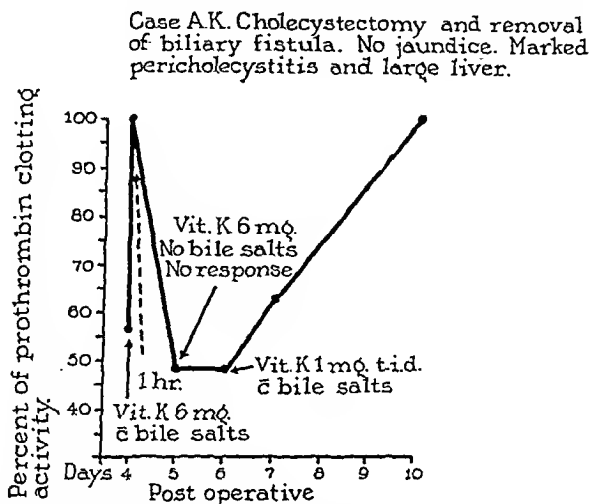


Fig. 2.—The prothrombin activity rose to normal one hour after a dose of 6 mg. of vitamin K and 2 Gm. of bile salts. The subsequent drop to the original low level within twenty-four hours was characteristic of patients with damaged livers. A second dose of 6 mg. of vitamin K, without bile salts, had no effect. A smaller dose of 1 mg. of vitamin K t.i.d., given with bile salts, produced a gradual rise to normal.

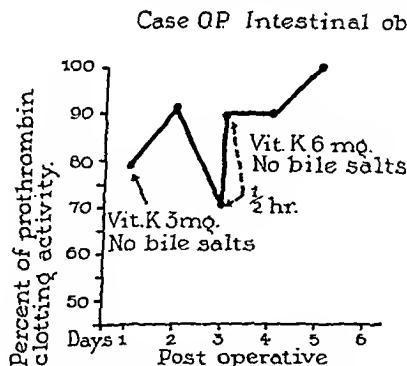


Fig. 3.—A reduction in prothrombin activity due to intestinal obstruction promptly returned to normal using vitamin K alone.

case of A. K. (Fig. 2), one hour after an initial large dose, the level rose from 57 to 100 per cent. In the case of M. R. (Fig. 1), a 75 per cent prothrombin activity increased to normal one-half hour after an initial 6 mg. dose. In three other cases there was a similar rise in one-half hour from 70 to 90 per cent, 66 to 80 per cent, and 74 to 90 per cent, respectively. Absorption of vitamin K is presumed to take place in the jejunum. The effect was so rapid that one might even

suspect absorption from the stomach. Since the absorption was so fast, we gave the vitamin to several patients who were being treated by constant gastric siphonage. The vitamin K was given by mouth, the duodenal tube clamped off for an hour, and the prothrombin level determined. The response was good in all cases.

An attempt was made to determine the duration of the effect of a single dose of the vitamin. The rise in prothrombin activity following a single dose was maintained in some cases for only twelve hours; in others, for three days; and in some it remained normal. We thought that clinically the patients with severe liver damage did not maintain the prothrombin level so well as did those with relatively good liver function. Undoubtedly there were exceptions to this. With such a variation in the maintenance of the plasma prothrombin one can be assured that the level is kept within normal limits only by repeated prothrombin determinations. Maintenance doses of 2 mg. of the vitamin, three times daily, are recommended if one is unable to perform the test very often. In the case of M. R. (Fig. 1) it was seen that the preoperative level of 75 per cent was increased to 100 per cent by a single 6 mg. dose. There was no abnormal bleeding. Not until the eighth postoperative day did the level begin to drop. On the tenth day it had reached 55 per cent. At this point therapy, to which the patient responded immediately, was started. This patient maintained a normal level for eight days postoperatively after only a single initial large dose of the compound.

A normal prothrombin activity before surgery does not indicate that the prothrombin percentage may not drop to dangerously low levels postoperatively. The fourth to the seventh day after operation was found to be the time when levels were lowest. Fig. 4 shows the postoperative prothrombin level in seven cases following biliary surgery. Five of these patients were jaundiced; two were not jaundiced. In all of them there was a significant drop in prothrombin activity between the fourth and seventh days, an interval that might be called the "critical period." Patient P. V. (Fig. 5) had a moderate degree of jaundice of four weeks' duration, due to a common duct stone. This patient was given daily doses of 3 mg. of vitamin K with bile salts preoperatively. On the fourth postoperative day the level dropped to 63 per cent. Six milligrams of the vitamin, with bile salts, were given, and in one-half hour the level was 100 per cent. This level was then maintained on a 3 mg. daily dose until the patient was on an adequate diet. A similar postoperative course was illustrated in the case of M. R. (Fig. 1).

We observed no toxic effects and no nausea or vomiting after the administration of the synthetic vitamin K. In this respect the synthetic vitamin K is far superior to the extracts which frequently caused

nausea and vomiting. One patient was given as much as 50 mg. of the compound in a twenty-four-hour period without any ill effects. However, the prothrombin level could not be elevated above normal even with this relatively massive dose. From this observation we supposed that there was a stabilizing effect, most likely through the liver, which prevents an increase in the plasma prothrombin level above normal.

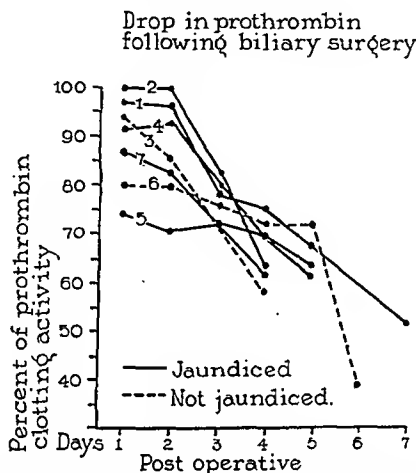


Fig. 4.—Following biliary surgery in both jaundiced and nonjaundiced patients, there was a significant drop in prothrombin levels between the fourth and seventh days.

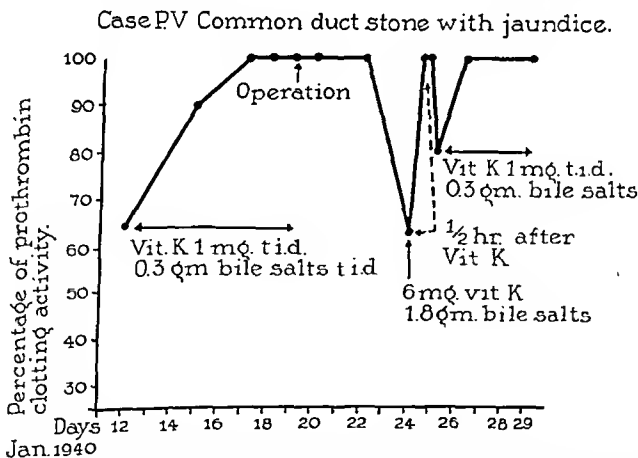


Fig. 5.—A normal prothrombin level was obtained by the preoperative administration of 1 mg. of vitamin K and 0.3 Gm. of bile salts t.i.d. The level dropped abruptly four days postoperatively. After a large dose of the drug, the prothrombin activity rose to normal in one-half hour. Subsequent daily administration was necessary to maintain the normal level.

In only one patient (Case M. M., Table I) did we find active bleeding (epistaxis and from the gums) as the result of jaundice. He had a cirrhosis of the liver with a moderate degree of jaundice. The prothrombin level was 63 per cent at the time vitamin K was given. An

initial 6 mg. dose brought the level to 100 per cent in one-half hour. The bleeding lessened but did not stop entirely. In our series of patients who were operated upon none was allowed to continue with low prothrombin levels without instituting vitamin K therapy. No abnormal bleeding occurred in these cases. Prothrombin determinations were made in various conditions in which bleeding was a characteristic manifestation (purpura, nephritis, leucemia, etc.). In none of these diseases was a delayed prothrombin time noted.

No correlation between the degree of jaundice or the duration of the jaundice and the plasma prothrombin level could be made. Five of our patients who had dangerously low levels did not have jaundice (Table II). Conversely, several severely jaundiced patients had normal prothrombin times (Table III). Thus, one may assume that

TABLE III  
JAUNDICED PATIENTS WITHOUT DIMINISHED PROTHROMBIN ACTIVITY

CASE	DIAGNOSIS	JAUNDICE		PROTHROMBIN ACTIVITY
		DURATION	DEGREE*	
1. H. S.	Toxic hepatitis	2 mo.	4	100%
2. A. W.	Toxic hepatitis	2 wk.	1	100%
3. C. S.	Pancreatitis	1 wk.	1	98%
4. A. B.	Cirrhosis of liver	1 wk.	2	92%
5. C. M.	Cirrhosis of liver	1 wk.	1	100%
6. G. N.	Cirrhosis of liver	1 wk.	1	100%
7. H. B.	Carcinoma of pancreas	1 mo.	2	90%
8. H. M.	Postappendectomy pylephlebitis	3 days	1	89%

\*Degree of jaundice: 1, slight; 2, moderate; 3, severe; 4, very severe.

jaundice in itself is not a criterion for the determination of prothrombin levels. From our observations it appears that any patient with biliary tract disease, with or without jaundice and with or without bleeding, should have a prothrombin determination if one wishes to eliminate entirely the danger of hemorrhage. Waddell and Guerrey<sup>19</sup> and Kato and Poncher<sup>20</sup> recently studied the relationship of vitamin K deficiency to hemorrhage in the newborn; they noted favorable results following vitamin therapy.

#### CONCLUSIONS

Twenty-three patients with a delayed prothrombin time were treated by oral administration of synthetic vitamin K. Twenty-two of these patients responded favorably. One case, in a terminal condition as the result of a carcinoma of the rectum, gave only a 5 per cent increase in the percentage of clotting activity.

The dosage of the synthetic compound recommended is an initial dose of 6 mg. with 2 Gm. of bile salts (six capsules of 5 gr. each). The plasma prothrombin level is then maintained with 3 to 6 mg. of vitamin K and 2 Gm. of bile salts daily.

Bile salts are necessary with the vitamin K compound for the patients who do not have bile salts secreted into the intestinal tract.

A pronounced response to the synthetic vitamin K almost invariably occurs within one-half to one hour.

The amount of vitamin K necessary to maintain a normal percentage of clotting activity varies individually; thus, prothrombin determinations are guides to maintenance dosage.

No nausea or vomiting and no toxic effects were observed following large doses of the synthetic compound.

In biliary tract surgery the fourth to the seventh postoperative day constituted the period when the prothrombin activity most frequently reached dangerously low levels.

Hypoprothrombinemia may occur with or without jaundice and with or without bleeding; no definite relationship between the degree or the duration of the icterus and the decreased prothrombin levels can be made. However, it is true that prothrombin levels approaching the bleeding levels will be encountered more frequently in jaundiced patients, particularly if considerable liver damage is present.

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# THE TREATMENT OF EXTERNAL FISTULAS OF THE PROXIMAL SMALL BOWEL

## A MEANS OF TEMPORARY MECHANICAL ANASTOMOSIS

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THE treatment of external fistulas of the upper small bowel has always been a serious and difficult problem as is evidenced by the multiplicity of methods which have been devised. The seriousness largely depends on the character and extent of the lesion and to a greater degree on its site. The higher the fistula in the upper small bowel, the greater its danger up to that level in the second part of the duodenum described as "the duct-bearing portion" and since spoken of as "the lethal line of Draper Maury." These fistulas, attended, as they usually are, by rapid loss of fluids, chlorides, and nourishment, produce a condition very similar to that caused by acute intestinal obstruction.<sup>2</sup> There rapidly ensues a rise in the blood nitrogen and a fall in the blood sodium and chloride ions.<sup>3, 4</sup> It has also been shown that the blood potassium rises in cases of complete intestinal fistula to toxic levels as found in acute intestinal obstruction, experimental adrenal insufficiency, and acute potassium poisoning.<sup>5</sup> This high potassium level is lowered by the administration of saline solutions. The loss of the digestive juices also is of importance as the loss of the pancreatic juice alone has been shown to be fatal.<sup>6</sup>

The occurrence of the fistula is distressing to the patient as it is realized immediately that something serious has occurred when with each ingestion of fluid by mouth there is an almost immediate gush of intestinal contents from the fistula. This mental distress is intensified by the physical one accompanying the ensuing digestion of the skin and tissue of the abdominal wall by the tryptic ferments.

Immediate operative surgical attack is not indicated in the great majority of cases due to the high mortality of about 50 per cent attending attempts at direct closure or side-tracking anastomosis. This mortality is directly related to the patient's poor general condition. Methods of conservative treatment are therefore indicated with the object of improving the patient's condition sufficiently to withstand the operative procedure. It may also be noted here that in certain cases these measures may in themselves result in healing.

The methods of treatment described may be classed as chemical, physical, mechanical, and surgical or combinations of these.

The chemical means are devoted to the minimizing or prevention of the digestive action of the juices on the patient's tissues by neutralization.

In 1929 Potter<sup>49</sup> described the use of beef extract and N/10 hydrochloric acid, reporting the healing of several incomplete fistulas by this means alone. He advised the building up of a wall about the external opening of the fistula or about the margins of the draining wound with gauze, impregnated with beef extract and laying inside this wall gauze dripping with N/10 HCl. The pancreatic juice is used up by activating the beef extract and is neutralized by the HCl. The excess HCl is used up on the beef extract rather than on the skin and tissues.

In 1930 CoTru<sup>5</sup> advised the use of kaolin, a colloidal absorbent for the electronegative trypsin. Its use has been reported frequently since, both alone and as an adjunct to other methods.

To lessen the skin excoriation the use of the continuous bath was advised by Cushing in 1899<sup>9</sup> and again recommended in 1919 by Ochsner,<sup>10</sup> who also found benefit from the feeding of egg white.<sup>11</sup> Cunningham<sup>12</sup> has advised the use of copper bronzing powder and in 1929 Rees<sup>13</sup> advocated dried milk as a dressing. Potter in 1932<sup>14</sup> suggested the use of the Bradford frame. With the opening of the fistula downwards and the intestinal wall pouting, the discharge from the fistula did not flood onto the patient's abdominal wall. In 1938 Dixon and Denterman<sup>15</sup> noted the relief obtained by the patient from the tanning of the eroded skin surface by 10 per cent tannic acid.

It is easy to understand that methods of blocking the fistulous opening were among the earliest treatments advocated. The first recorded case is that of Reybard,<sup>16</sup> who used a wooden button in the lumen of the gut tied to a crossbar on the abdominal wall by a suture passing through the fistula. A button of leather was later recommended by Kleybolte in 1842.<sup>17</sup> Gauze soaked in oil has been used by Rigby,<sup>18</sup> Hendon,<sup>19</sup> Fechen,<sup>20</sup> and Stadler<sup>21</sup> to block the fistulous opening, and chewing gum recommended by Judd and Phillips<sup>22</sup> in those small fistulas which are not serious but leak and cause excoriation. Johnston<sup>23</sup> described the use of two small inflatable balloons placed about 1.5 cm. apart on a two-way catheter as a temporary closure. The inner balloon is inserted into the lumen of the bowel and inflated, then withdrawn into the fistulous tract until the second balloon appears on the surface. This outer balloon is then inflated to hold the first balloon in place. The inner balloon tightly wedged in the fistulous tract effectively closes the opening. In 1917 Dowd<sup>24</sup> described a double metallic button which has been used successfully also by Mayo<sup>25</sup> and Cattell.<sup>26</sup> Kappis<sup>27</sup> in 1911 used a T-tube with the straight part of the tube providing a channel between the upper and lower parts of the bowel with the right-angled part protruding through the fistula, blocking it and providing drainage for overflow. This method has been used by Kaehler<sup>28</sup> and Pamperl<sup>29</sup> and also by Ahrens,<sup>30</sup> who points out that the straight part of the tube tends to depress the spur on the mesenteric side of the bowel.

As late as 1938 Marshall and Lahey<sup>31</sup> pointed out the lifesaving value of ordinary buttons, one on the inside of the bowel tied to another on the abdominal wall, as an emergency treatment. Hartzell<sup>32</sup> in the same year described in detail how he makes a disk of soft rubber to fit accurately the inside of the bowel at and about the fistulous opening. The rubber disk is held in place by a thread fixed externally. He finds this method particularly valuable where there is a fairly large opening in a presenting knuckle of bowel.

The use of suction in some form has been found by Cheever,<sup>33</sup> Lahey,<sup>34</sup> Walters, Kilgore, Bollman,<sup>3, 4</sup> and Ochsner<sup>10</sup> to be a very practical means of dealing with the fluids from the afferent loop. It has been used for the simple removal of the offending discharge and also for the collection of the fluids extruded for readministration to the patient.

Cameron in 1923<sup>35</sup> reported the use of an electric suction apparatus connected to a catheter with several additional holes inserted into a duodenal fistula following gastric resection with cure.

Bohrer and Milici (1931)<sup>36</sup> in the treatment of duodenal fistula advised dilating the opening and introducing into it a half-inch fenestrated rubber tube to act as a reservoir. Into this large tube was placed a small rubber catheter attached to a vacuum bottle. The discharge was thus removed as quickly as it accumulated. They advised also that the vacuum be maintained by a water pump as all electric suction will become heated by continuous use. They discontinued all food by mouth except water, which dilutes the discharge and allows the suction to work better. Their patients were fed by nutrient enemas, glucose by vein, or hypodermoclysis.

In 1937 Tenopyr and Shafiroff<sup>37</sup> reported a method combining chemical and mechanical means whereby the intestinal contents were removed from the bowel without skin irritation. A Murphy drip tube is fitted into the center of a large soft rubber doughnut pessary which is bound tightly over the fistula by a bandage about the body, the tip of the Murphy drip tube just entering the opening of the fistula. Kaolin is packed between the pessary and the skin. A Wangensteen suction apparatus attached to the tube removes the fluid into a container by the bed.

Another method combining the use of kaolin and suction was described by Dixon and Deuterman in 1938.<sup>15</sup> They place a suction tube through a wall that is built about the external stoma. The wall is constructed of adhesive tape and a paste made of kaolin and water on the freshly cleansed skin. The tip of the soft rubber fenestrated suction tube is placed partially inside the external stoma of the fistula.

The feeding of these patients and the return of the fluids collected have been accomplished by various means.

The introduction of liquid food by jejunostomy has been recommended by Bohrer and Milici,<sup>36</sup> McGuire,<sup>38</sup> Lewisohn,<sup>39</sup> Erdman,<sup>40</sup> Kelling,<sup>41</sup>

Pannet,<sup>42</sup> Dixon and Deuterman.<sup>15</sup> Einhorn<sup>43</sup> passed a duodenal tube beyond the fistulous opening for feeding. In 1927 Marogna<sup>44</sup> reported passing a long tube through the fistula into the jejunum through which food was introduced. Erdman in 1921<sup>40</sup> reported in the treatment of duodenal fistula the use of continuous suction into a bottle by the bed, and the return of these materials through a jejunostomy tube through which the patient also was entirely fed. This patient recovered but developed a parotitis which resolved without external suppuration. He also introduced saline solution by a Murphy drip into the jejunostomy tube. Dixon and Deuterman (1938)<sup>15</sup> also advocated this method.

Fox in 1936<sup>45</sup> suggested collection of fluids by suction and their return by proctoclysis.

Wilkie<sup>46</sup> introduced two catheters, one in the afferent connection with another in the efferent loop. Volkman<sup>47</sup> and Peet<sup>48</sup> found this method valuable.

Where the lesion is small or is a simple fistulous tract leading to bowel which is in continuity, the problem is a less serious one and in these cases simple suction, the use of neutralizing substances, or means of temporarily blocking the fistulous opening may result in healing. Sometimes the disagreeable leak with accompanying digestion of surrounding skin is the most troublesome problem as the patient's nutrition and metabolism may not be seriously impaired.

Where, however, there is complete severance of continuity of the upper small bowel or a very large opening, the problem becomes one of more emergent character and lack of adequate treatment is rapidly fatal. In these cases all the contents of the small bowel are discharged on the skin surface; the loss of nourishment and fluids is total and hypochloremia with toxemia rapidly ensues. Digestion of the abdominal wall is rapid and extensive.

Such a case occurred in the wards of the Montreal General Hospital in 1929. A summary of the history is as follows:

CASE REPORT.—Mrs. H. P., aged 46 years (Hospital No. 7295/28), was admitted to the Montreal General Hospital, Dec. 19, 1928, with a perforated diverticulum of the sigmoid colon. The perforated mass of bowel was extraperitonealized as a colostomy through the exploratory wound and though very ill for a time due to the fecal generalized peritonitis, she recovered. Closure of the colostomy was later done and on the third day after this operation leakage through the wound was noted, and by the seventh day examination of the wound showed six open ends of small bowel presenting in pairs at intervals in the wound. The intestines, herniating through the disrupting wound, had pressed upon the silkworm gut sutures used to close the skin and had been completely cut through in three places. The skin about the wound was excoriated and the patient's condition deteriorating. Saline and glucose solutions were given intravenously. The openings of the upper and lower portions of bowel were determined, and, using the open end of a tube over the proximal opening, continuous suction was applied. The collected fluids, with other fluid nourishment, were fed back into the distal loop by a catheter at intervals of two hours by day and three hours by night. Fluids by mouth were discontinued. All varieties of substances

then available were employed on the abdominal wall in efforts to prevent its digestion, but with each peristaltic wave of the upper jejunal loop intestinal contents with digestive juices gushed over the abdominal wall as the ordinary suction apparatus was unable to cope with it. Especially was this so when occasionally anything was given by mouth. Despite all efforts and treatments, the patient gradually and progressively deteriorated, became extremely emaciated, and required stimulants at frequent intervals to keep her alive. It was quite obvious that unless something more could be done she would very soon die. The digestion of the skin of the abdominal wall was very extensive. All available superficial veins eventually became thrombosed and fluids had finally to be given by subcutaneous injection or by cutting down on deeper veins.

After trying out several methods of re-establishing the continuity of the small intestine by external means, at this point, thirty-eight days postoperative, an apparatus was devised which was successful. This device removed mechanically all the contents of the upper loop and automatically transferred them to the lower loop without any spilling, feeding them slowly into it so that they were readily absorbed. There was no further loss of electrolytes and digestive juices from the intestinal tract, and with the additional morale given the patient by being able to take fluids and nourishment by mouth, there was rapid improvement. All varieties of clear fluids could be given and the patient was encouraged to drink them freely as the apparatus had no difficulty in handling large amounts. Practically the only precaution necessary was to forbid giving foods which would block the holes in the tubing. Milk could not be given as it is coagulated in the stomach. Nourishment, in addition to that taken by mouth, was given through the apparatus in the form of glucose solution. As the transfer of fluids from one loop to the other was continuous and automatic, a minimum of attention was required. Minor adjustments to the tubing in the bowel were all that was necessary, and this about once a day.

Subcutaneous fluids were discontinued in twenty-four hours and stimulants were decreased on the fourth day. The intestinal contents did not come in contact with the abdominal wall; there was no soiling and the digested areas rapidly healed so that by the tenth day the abdominal wall was "dry and almost healed."

On the nineteenth day after the apparatus was put into use the patient was sufficiently recovered to withstand operation. Preceded by blood transfusions, a successful shortcircuiting anastomosis was performed through a completely healed abdominal wall.

At a subsequent operation months later, the shortcircuited loops of bowel opening onto the abdominal wall were excised.

The apparatus is activated by continuous suction and its construction is simple. A fenestrated rubber tube 5 to 6 inches in length (the tip of a large rectal tube with additional holes cut in its sides works admirably) is inserted into the proximal or afferent loop and held in by tapes tied about its outer end secured to adhesive strips on the sides of the abdomen, or to a band about the back. Into this "well" is inserted a soft rubber catheter which has had several additional small openings made in its terminal 2 to 3 inches. This catheter is attached by rubber tubing to the top of a reservoir which is a glass tube  $1\frac{1}{4}$  inches in diameter and 2 feet long with a rubber stopper at either end. This glass tube is held in a vertical position by a laboratory clamp and stand set on a bedside table. Inserted also into the upper end of this closed reservoir

is a tube leading to the suction. From the bottom of the apparatus a single tube leads directly to another soft rubber catheter which is inserted for almost its full length into the distal or efferent loop of bowel.

When suction is applied, small amounts of fluid and air rise alternately in the afferent tube, spilling over into the reservoir; the continuous column of fluid in the reservoir and the efferent tube causes the fluids to flow slowly and continuously into the efferent loop of bowel. Glucose solution may be added to the intake by inserting a T-tube in the afferent rubber tube just before it empties into the reservoir. A donehe can is



Fig. 1.—Photograph of original apparatus in use.

connected to it through a Murphy drip and the rate of flow controlled by a stopcock. Only a moderate amount of continuous suction is required to activate the apparatus. The suction system with which our surgical wards are equipped was used in this case, but suction from a water pump would work very well.

The importance of restoring the fluid and electrolyte balance cannot be overestimated. This phase of treatment has been emphasized and detailed recently by Collier and Maddock<sup>50</sup> so will not be further discussed here. There would appear, however, to be some factors contained in the normal digestive juices which cannot as yet be replaced

by intravenous therapy but are returned to the patient by the restoration of the fluids lost through the fistula and contribute markedly to recovery.

It would seem that the only indication for surgery in the early treatment of these cases would be in those where an obstruction is present below the fistula or where, for some other reason, a soft rubber catheter cannot be passed. If it is impossible to pass a catheter into the lower loop, a jejunostomy should be performed to receive the efferent catheter. Where the opening is in the side of presenting bowel, the fenestrated tube or "well" may be inserted in the afferent side of the spur and the efferent catheter into the distal one. Where the fistulous tract is long and the opening high in the intestinal tract, the "well" may be inserted into the fistula and the efferent tube led to a duodenal tube whose tip has been passed well beyond the fistulous opening as suggested by Einhorn.

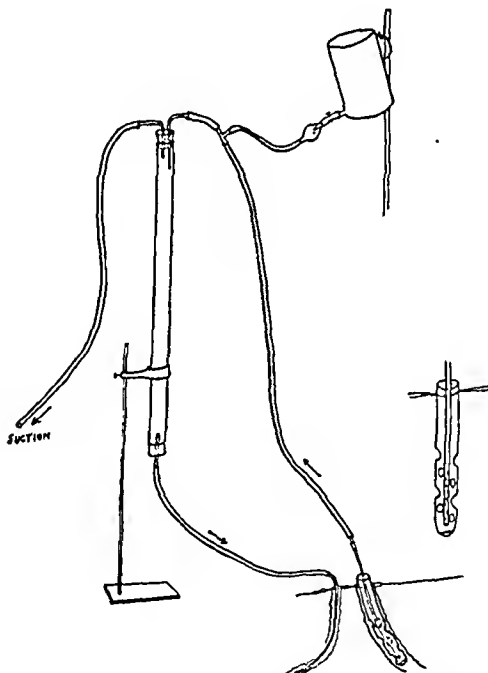


Fig. 2.—Diagram of apparatus showing: fenestrated tube forming "well" in proximal loop or in fistula, with fenestrated catheter in place; the connected irrigating can from which glucose solution, for additional nourishment, enters the apparatus; glass tube reservoir; catheter inserted into the efferent loop or into a jejunostomy; tube leading to suction. The direction of circulation is indicated by arrows.

#### SUMMARY

1. The pathological physiology of proximal external small bowel fistulas is briefly summarized.
2. The various methods used in their treatment are reviewed.

3. A simply made apparatus for temporary mechanical anastomosis, activated by continuous suction, is described.
  4. A case of multiple complete jejunal fistulas, in which the above apparatus was successfully used, is reported.
- Since this article was submitted for publication, two more cases have been successfully treated by this method on the surgical service of Dr. F. B. Hurd at the Montreal General Hospital.

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# PATHOLOGIC STUDY OF HYPERTROPHIC ARTHRITIS OF THE HIP\*

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THE disease of the hip characterized clinically by moderate or severe pain on motion, with creaking and grating, with no marked deformity except in very advanced cases, and with stiffness of the joint after periods of rest and variously known as hypertrophic arthritis, degenerative arthritis, arthritis deformans, osteoarthritis, morbus coxae senilis, and by many other terms is one of the common causes of discomfort and disability in the middle and later years of life.

The advances made in the study of its causation and prevention have been negligible in comparison with those made in the same fields in other diseases, or even in other forms of arthritis, and this is particularly true in proportion to the amount of disability caused by it. In a review of the literature on arthritis for 1937, Hench found only six articles of more than 700 in which hypertrophic arthritis was the sole or chief topic, and he came to the conclusion that it "remains a neglected stepchild in the family of rheumatism."

It might be assumed from the foregoing discussion that the treatment of hypertrophic arthritis is in as sad a state as is our knowledge of its causation, since the efficacy of therapeutic procedures for any disease depends largely on a thorough knowledge of its causative factors. Such is the case, although within comparatively recent years numerous procedures of one sort or another have been devised to alleviate the symptoms. The various forms of physical therapy are still the most common forms of treatment and in most cases will give a considerable degree of temporary relief. Diets, vaccines, and other similar methods, on the whole, are useless. Surgical procedures, consisting of manipulation under anesthesia, cheilotomy and remodeling of the head of the femur, acetabuloplasty, and forage of the head and neck of the femur, are sometimes indicated in painful hypertrophic arthritis. Arthrodesis, according to Henderson, is usually refused by the patient although it is certainly the procedure of choice in those patients whose occupations include heavy labor. Roentgen therapy is sometimes used, with occasional favorable results.

## ETIOLOGY OF HYPERTROPHIC ARTHRITIS

Inasmuch as the cause is not definitely known, it was thought that a brief review of the most widely accepted hypotheses might aid in under-

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standing or interpreting the various pathologic changes which are found. It must be remembered in a discussion of the etiology, if not of the pathology, that hypertrophic arthritis may be either primary or secondary and that the latter may be the sequela of traumatic arthritis or of the various forms of infectious or metabolic arthritis. Some authors, notably O'Reilly, have maintained that the secondary types should not be included in a discussion of hypertrophic arthritis, since they are not the true primary type of osteoarthritis. However, the pathologic changes are the same, and they will be considered together in this paper.

Trauma of a localized form must be given a place of prominence in any discussion of the etiology. Opinions vary from that of Fisher,<sup>3,4</sup> who said that in this group it forms almost the sole etiologic factor, to that of Jones, who expressed the opinion that it may be a determining but not an actual cause. Fisher expressed the opinion that the most important type of trauma in the production of hypertrophic arthritis is the frequently repeated microtrauma, rather than a single, severe contusion of a joint. He also pointed out the fact that there may be posttraumatic inflammation of a joint without the presence of infection. When posttraumatic intra-articular changes do occur, they are hypertrophic in character and pathologically the same as primary (senescent) hypertrophic arthritis. When the etiologic factor is a single acute contusion, it may be years before the hypertrophic changes appear, at which time it may be impossible to draw an analogy between a possibly youthful victim of trauma and a senile patient with hypertrophic arthritis. If such an acute injury resulted in a residual deformity, however, and particularly if at the time the patient presented himself the arthritis were monoarticular or more severe in the traumatized joint than in untraumatized joints, such an analogy would be logical. In a recent review of 150 cases of hypertrophic arthritis of the hips, 20 per cent gave a definite history of previous severe trauma of the involved joint.

The association between hypertrophic arthritis and arteriosclerosis was noted by many of the older physicians, and for a time this was one of the favorite explanations for the occurrence of the disease, but any direct evidence that osteoarthritis may occur secondarily to arteriosclerosis is very scanty and most modern observers discount this hypothesis. Numerous experiments have been done in an effort to support this hypothesis, however, notably those of Wollenberg, who tied the patellar vessels of a dog and noted that this was followed by overgrowth of the patella, with evidence of degeneration of the articular cartilage and hypertrophic changes. Fisher subscribed to this hypothesis to the extent that he admitted the possibility that arteriosclerotic changes may contribute to the decreased nutrition of degenerating cartilage, but, in view of the absence of sclerosis in early cases of osteoarthritis, he expressed the opinion that the coexistent arteriosclerosis and osteoarthritis have a common cause. Hench found in the literature on osteoarthritis

that the incidence of arteriosclerosis was no greater in osteoarthritis than in a similar age group without osteoarthritis and came to the conclusion that little or no support could be found for the hypothesis.

The inclusion of hypertrophic arthritis in the great group of diseases formerly classified under the single heading "rheumatism" and its consequent association in the minds of physicians and laymen with the infectious types of arthritis naturally have led to the formulation of numerous hypotheses of its causation based on the premise that it, too, was the result of infection. At the present writing, no organism has been found in osteoarthritis, and in view of the clinical course of the disease it seems unlikely that any specific organisms ever will be found within the joint. On the other hand, it is well recognized that in the more destructive types of infectious arthritis new bony formations and changes are encountered which are characteristic of hypertrophic arthritis. Kaufmann stated that it might follow infectious arthritis or chronic purulent synovitis, and Albee and Preston<sup>1</sup> said that it may become engrafted on healed arthritis of a tuberculous or pyogenic type. In general, the various authorities consulted agreed that osteoarthritis might supervene in a joint previously injured by bacterial invasion but, other than that, bacterial infection seemed to have no part in the picture.

There may be some obscure bond between osteoarthritis and the ductless glands, but it has never been definitely proved that the incidence of endocrine dysfunction is greater in those suffering from osteoarthritis than it is in others in the same age group who do not present symptoms of arthritis. Fisher expressed the opinion that disordered endocrine function plays an important part in osteoarthritis, particularly the type seen in women at the menopause. He stated further that the same type of arthritis may be found in younger women after an artificial menopause, and Llewellyn said that the resistance of a patient to osteoarthritis is lowered after thyroidectomy or the exposure of the thyroid to roentgen rays. According to both McCarrison and Llewellyn, osteoarthritis is more common in regions of endemic goiter than one would normally expect. Favorable results are sometimes obtained by giving thyroid to osteoarthritic patients, but the probabilities are that the improvement noticed is due to a general improvement in body economy rather than to any specific effect of the thyroid hormone on the arthritis.

#### PATHOLOGIC CHANGES AS DESCRIBED IN THE LITERATURE

*Changes in the Articular Cartilage.*—Ziegler expressed the opinion that the cartilage may still be intact at a time when there is already considerable deformity of the head of the femur. On the other hand, Fisher said that the first change observed by him is an alteration in the normal color and translucent appearance of the cartilage, particularly the central portion where he assumed that the circulation is inadequate. Jones bore him out in his assertion that the first changes are at the

standing or interpreting the various pathologic changes which are found. It must be remembered in a discussion of the etiology, if not of the pathology, that hypertrophic arthritis may be either primary or secondary and that the latter may be the sequela of traumatic arthritis or of the various forms of infectious or metabolic arthritis. Some authors, notably O'Reilly, have maintained that the secondary types should not be included in a discussion of hypertrophic arthritis, since they are not the true primary type of osteoarthritis. However, the pathologic changes are the same, and they will be considered together in this paper.

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jacent trabeculae, particularly in the regions of eburnation. According to MacCallum, when the bony surface is exposed, the resultant irritation due to the motion of the joint sets up the formation of new bone, the surface layers becoming hard and compact. If a large enough area of bone is exposed, it may be worn away deep into the epiphysis, resulting finally in a mushroom-shaped head.

Fisher observed that the exposed surface of bone became "polished and glistened like porcelain," and that frequently its surface was marked with grooves which he thought were produced by the epiechondroses or periechondroses of the opposed articular surface. He also said that the subchondral plate may show evidence of thickening and increased density before the cartilage has disappeared, and Ziegler



Fig. 1.—Periarticular ecchondrosis, with formation of new bone, just below its center, and increased thickness of the subchondral plate (Case 17,  $\times 25$ ).

thought he observed these changes even before the cartilage showed evidence of degeneration. Stockman and Shattock studied the surface of the eburnated bone and observed that the Haversian canals opened on its surface as the bone was gradually worn away, thus proving, if there were any doubt, that the eburnated surface is composed of true bone. Stockman also expressed the opinion that the Haversian canals were invaded by many small blood vessels, possibly resulting in atrophy and absorption of the underlying bone.

Allison and Ghormley, besides observing some of the foregoing pathologic changes, also noted an increased thickness of the trabeculae subjacent to the regions of eburnation.

*Pathologic Changes in the Bone Marrow.*—The characteristic changes observed in the marrow consisted, briefly, of fibrosis or its variations.

center of the cartilage. The cartilage soon begins to show some microscopic changes with an alteration in the staining reaction of the matrix, but with as yet no changes in the cartilage cells. At a slightly later stage, according to Fisher, fibrillation of the matrix and degeneration of the cells near the articular surface of the cartilage appear. He pointed out the obvious fact that there is no invasion of the cartilage by fibrous tissue at this stage and stated that by "fibrillation" he meant a mere splitting of the matrix. As the degeneration of the cartilage progresses, the cellular elements degenerate and one may observe deposits of calcium salts in the deeper layers of the matrix. Finally, the cartilage may be completely worn away from the subchondral plate.

According to MacCallum the changes are predominantly in the cartilage, which first becomes fibrillated or plushlike, and Stockman observed that the cartilage was early dulled in color, suffering a loss of its normal "polish," subsequent to which small elevations appeared over its surface with larger irregular masses at the margins of the joint, consisting of spongy bone covered with cartilage. The matrix at this stage may be normal or fibrillated, and there is active proliferation of the cartilage cells. Later the matrix becomes definitely fibrillated, the more superficial layers horizontally, the deeper layers vertically, and the top layer is worn away, leaving the lower furlike layer with actively proliferating cartilage cells which are discharged into the joint space.

According to Fisher, the small elevations appearing over the surface of the cartilage, and observed by Stockman, are properly called epia-articular eechondroses, in distinction from peria-articular eechondroses, and are the result of invasion of the deeper layers of the cartilage by osteoid tissue with the formation of new bone, or the result of ossification in the cartilage itself which has previously undergone hyperplasia of some sort. It is pointed out that these eechondroses may become detached to form loose bodies in the joint.

Fisher expressed the opinion that the more competent circulation at the periphery of the joint explains in large part the formation of the peria-articular eechondroses (Fig. 1). He observed that, when the degeneration of the central cartilage was well advanced, the marginal cartilage showed signs of hypertrophy, producing the condition known as "lipping." These peria-articular eechondroses are eventually invaded by osteoid tissue, as were the epia-articular eechondroses, and become ossified to form a chondro-osteophyte. They may later become eburnated under the proper conditions and have been known to break off to form loose bodies in the joint cavity. According to Nichols and Richardson,<sup>13, 14</sup> these marginal exostoses usually appear first in the capsular attachments, and they agree with Fisher that they form an actual increase in the size of the articular surface.

*Pathologic Changes in the Bone.*—The most striking change in the bony structures is the thickening of the subchondral plate and its sub-

small areas of grayish tan discoloration were seen. Proliferation of the marginal cartilage was present in every case in which part of the margin of the articular surface was present, and in these regions the cartilage seemed to be in a better state of preservation. It was not as soft as was the cartilage in the central areas of the articular surfaces, was pearl gray in color, and in a few instances gave a definite translucent appearance. Numerous small pits were observed in some of the sections, principally in the region of the central articular area.



Fig. 2.—Vertical fibrillation of the cartilage matrix (Case 1,  $\times 90$ ).

Numerous areas of eburnation were found, varying in size from a few millimeters to several centimeters, and they invariably presented a highly polished, glistening appearance. On cross section of the specimens it was seen that the subchondral plate was thickened in most cases in the eburnated areas, and the cancellous portion of the bone also seemed to be more abundant subjacent to these areas. These changes were not observed in those regions still protected by the articular cartilage.

No definite conclusions could be reached as to the condition of the marrow. Synovial tissue, when present in large enough amounts to examine grossly, seemed to be firm and fibrous in character.

The microscopic examination revealed degeneration of the articular cartilage in every instance. Some beautiful examples of both longi-

So-called cysts filled with loose fibrous tissue were seen by most of the observers, and in many instances the marrow had apparently been replaced by fat tissue. The fibrosis of the marrow spaces was apparently particularly evident in the region of the subchondral plate.

*Pathologic Changes in the Synovial Membrane and Capsule.*—At the same time that lipping of the articular margin appears (Fisher), the synovial membrane proliferates with the formation of new villi and hypertrophy of the old villi. Later in the disease the membrane may become atrophic and comparatively smooth. When examined microscopically, the villi are seen to be very vascular and most of the synovial tissue has been replaced by fibrous tissue. Cartilaginous bodies may form in the villi, later to be broken off to form loose bodies in the joint cavity.

Changes in the joint capsule were apparently not observed, although Fisher mentioned that the capsule may "migrate" to accommodate itself to the changing shape of the head of the femur.

#### PATHOLOGIC OBSERVATIONS ON OUR MATERIAL.

The percentage frequency of different pathologic features in the nineteen cases on which this paper is based is shown in Table I.

TABLE I

PERCENTAGE FREQUENCY OF DIFFERENT PATHOLOGIC FEATURES IN 19 CASES OF HYPERTROPHIC ARTHRITIS OF THE HIP

PATHOLOGIC FEATURES	NO. OF CASES	PER CENT OF TOTAL	CORRECTED PERCENTAGE*
Degeneration of articular cartilage	15	79	100
Fibrillated cartilage	13	68	87
Pitted cartilage	12	63	80
Proliferation of marginal cartilage	9	47	100
Increased calcification of deeper cartilage matrix	15	79	100
Increased thickness of subchondral plate	15	79	100
Eburnation	11	58	73
Increased thickness of trabeculae subjacent to eburnation	11	58	100
Atrophic marrow	16	84	100
Osteoid tissue formation	16	84	100
Fibrosis cystica	10	53	66
Fibrous synovial membrane	15	79	100
Arteriosclerosis	11	58	58
Collections of lymphocytes in synovia or marrow	0	0	0

\*In computing the corrected percentage, those cases were eliminated in which a particular type of tissue change did not appear in the specimen; for instance, eburnation appeared in only 58 per cent of the 19 specimens studied, but it appeared in 73 per cent of the 15 specimens in which at least part of the articular surface was present.

The gross examination of the specimens studied revealed evidence of degeneration of the articular cartilage in every case in which cartilage was a part of the specimen. For the most part, the cartilage was dull and had lost its normal translucent appearance, and on a few specimens

fibrous tissue or pannus in which there was no evidence of lymphocytic infiltration. Most of the cartilage cells were pyknotic, and this was particularly true of those cells near either surface of the cartilage. No definite evidence of proliferation of the cells was found in any of the degenerating cartilage. In numerous instances the cartilage adjacent to the subchondral plate had been invaded by fibrous tissue from the marrow which, in some cases, had dedifferentiated into osteoid tissue with evidence of the formation of new bone. Increased deposition of calcium salts in the deeper matrix was found in all the specimens (Fig. 3).

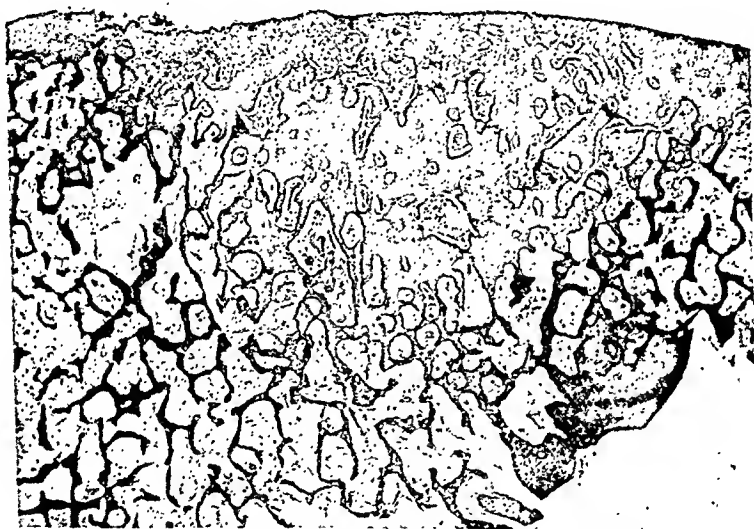


Fig. 5.—Eburnation with increased thickness of the subchondral plate and its subjacent trabeculae, which have united to form almost a solid pyramid of bone extending into the head of the femur. Marked activity of osteoid tissue in the marrow spaces included in this region (Case 17,  $\times 6$ ).

The most striking change noted in the bone was the increased thickness of the subchondral plate (Fig. 4), chiefly in the regions of eburnation. Slight increases in its thickness were noted subjacent to areas where the cartilage was markedly degenerated, but under areas that were still protected by a moderately thick layer of cartilage the subchondral plate was not thickened and, in some instances, was even thinner than normal. In the regions of eburnation there was usually extensive formation of new bone in the marrow spaces immediately subjacent to the subchondral plate with increased thickness of the trabeculae as well as of the plate. It was evident that the marrow had been replaced by fibrous tissue which had dedifferentiated into osteoid tissue with subsequent calcification. This chain of events was almost never seen in those areas which were still protected by a layer of cartilage, no matter how degenerate, but it was observed that in numer-

tudinal and vertical fibrillation of the matrix were seen, accompanied in most instances by irregular staining qualities (Fig. 2). The longitudinal fibrillations were much finer in character than the vertical fibrillations, with an occasional pyknotic chondrocyte lying among the "fibers" here and there. Pitting of the cartilage was observed in some of the specimens, and some of them appeared to be filled with a loose

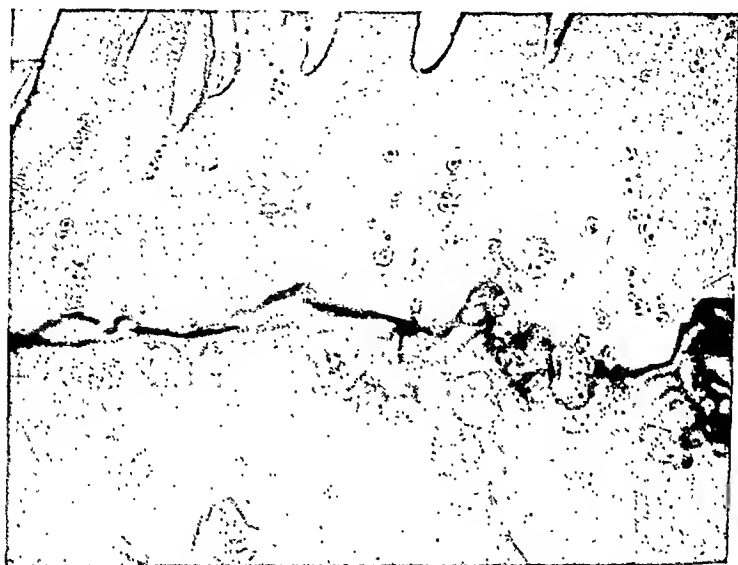


Fig. 3.—Increased deposition of calcium salts in the deeper cartilage matrix (Case 3,  $\times 90$ ).



Fig. 4.—Fibrillation of the cartilage and increased calcification of the deeper matrix, with increased thickness of the subchondral plate (Case 11,  $\times 95$ ).

ous spots the subchondral plate and lower cartilage matrix had been invaded by small wicks, so to speak, of fibrous tissue which, in some instances, had dedifferentiated into osteoid tissue with the formation of small islands of bone in the cartilage matrix adjacent to the subchondral plate. This latter process seemed to be an endochondral ossification rather than the intramembranous ossification observed under the areas of eburnation. The manner in which the trabeculae under the eburnated areas had thickened and "gathered together," so to speak, to form a support for the subchondral plate was remarkable, and in two instances almost a solid pyramid of bone was observed extending into the cancellous portion of the head (Fig. 5). Many of the bone cells, particularly in the areas of eburnated bone, were pyknotic, and Haversian canals were observed opening onto the surface of the eburnated areas.



Fig. 8.—Atrophy of marrow, eburnation, and thickening of trabeculae and subchondral plate (Case 7,  $\times 4$ ).

The great majority of the marrow spaces had become filled with fat tissue although, as described previously, the spaces adjacent to the subchondral plate were frequently filled with either osteoid tissue or fibrous tissue (Fig. 6), giving the appearance of osteitis fibrosis cystica. In a



Fig. 6.—Intramembranous ossification in a marrow space subjacent to an area of eburnation (Case 3,  $\times 80$ ).



Fig. 7.—Marked arteriosclerosis and fibrosis of the synovial membrane (Case 1,  $\times 110$ ).

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few fields fairly normal marrow tissue was seen, but even here there had been much replacement by fat cells.

The synovial tissue invariably showed evidence of fibrosis, with markedly increased vascularity (Fig. 7). The sclerosis of the vessels was graded according to the method of Kernohan, Anderson, and Keith<sup>9, 15</sup> and varied from no evident sclerosis in 5 of the 19 cases studied, to Grade 3 sclerosis on a basis of 1 to 4 in 2 of the cases. Of the remaining 12 cases, one was graded 0 to 1, two were graded 1, two were graded 1 to 2, five were graded 2, and in two the grade was not stated.

Fig. 8 shows the association of several of the foregoing changes in the same case.

#### SUMMARY AND CONCLUSIONS

Nineteen specimens of hypertrophic arthritis of the hip have been studied, and the pathologic changes observed have been described. It was found that:

1. The initial degenerative changes appear in the cartilage and are characterized by fibrillation, pitting, degeneration of the cartilage cells, and increased calcification of the deeper matrix.

2. The marginal cartilage proliferates and shows few of the signs characteristic of degeneration.

3. As the cartilage disintegrates and is worn away, the bone is exposed and becomes eburnated with thickening of the subchondral plate and the subjacent trabeculae by means of intramembranous ossification.

4. The subchondral plate may or may not be thickened. The trabeculae are almost never increased in size in those areas that are still protected by cartilage, and most formation of new bone in these areas is of the endochondral type.

5. The normal marrow is replaced by fat or loose fibrous tissue which, in some instances, dedifferentiates into osteoid tissue.

6. The synovial membrane is invaded by fibrous tissue with markedly increased vascularity.

7. Little evidence was found to support the hypothesis that arteriosclerosis is an etiologic factor of osteoarthritis.

8. Finally, no collections of lymphocytes were found which are characteristic of the infectious types of arthritis.

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Recurrence took place, and tumors of varying sizes about the shoulder were removed on Dec. 22, 1923, July 15, 1925, and Nov. 14, 1925. Radium was implanted into the wound on each occasion, the largest exposure being given on Nov. 14 when 200 mg. of radium were allowed to remain for forty-eight hours. All during this time the patient stoutly refused to submit to an operation that would sacrifice the arm. From the large doses of radium used, severe radium burns resulted. However, on March 29, 1926, the patient returned with a beginning gangrene of the fingers. The arm was cold and cyanotic, and the radial pulse was barely perceptible. A large recurrence had taken place in the axilla which had involved the axillary vessels. On March 31, 1926, the arm, including the clavicle, was removed, but a wide dissection of the axilla did not seem justifiable at this time because of the patient's rather poor condition. One month later, on April 26, 1926, the patient meanwhile having greatly improved, a very radical removal of the involved area was carried out. The subclavian vessels were ligated medial to the anterior scalenus muscle. The cervical nerves giving rise to the brachial plexus were severed in the same region. A



Fig. 1.—Showing scars of previous operations and a large recurrence on the posterior aspect of the shoulder.

wide circle of skin was made and carried down to include a large portion of the pectoralis major and minor muscles and the anterior edge of the trapezius muscle. A portion of the second rib that had become necrotic was removed, along with the axillary contents, well below the recurrence and down to the chest wall. The dissection was carried so high on the subclavian vein that injury to the thoracic duct took place, as evidenced by a spill of considerable chyle into the operative wound. A gauze pack was placed in the area from which chyle was seen to ooze, and, when it was removed several days later, no further discharge of this nature was seen. Following the operation an uneventful recovery took place, and no evidence of recurrence has since been noted. This individual has carried on with his work as a court stenographer and in spite of the loss of the arm and shoulder is able to hunt and shoot birds with considerable accuracy. Many details in the conduct of this case have been omitted for the sake of brevity, such as x-rays for possible metastasis, transfusions, and minor complications.

## THE TREATMENT OF TUMORS OF THE SHOULDER REGION BY INTERSCAPULOTHORACIC AMPUTATION

J. E. STRODE, M.D., AND E. A. FENNEL, M.D., HONOLULU, T. H.

*(From the Clinic)*

EXCEPTIONALLY the occasion arises where it seems justifiable to remove the arm with the shoulder girdle in the treatment of tumors when less drastic measures have proved to be ineffective. The loss of this part of one's anatomy is not only extremely crippling and disfiguring, but the extensiveness of the operation is of sufficient magnitude to carry with it an appreciable mortality. Therefore, it is a point requiring considerable surgical acumen to determine correctly the time when less radical measures should be abandoned in favor of interscapulothoracic amputation.

Occasionally this operation may be indicated following trauma to the shoulder, rarely for an inflammatory process such as that described by Mileh,<sup>1</sup> but undoubtedly the most frequent indication will continue to be a relatively benign radioresistant tumor that cannot be widely enough excised locally, due to nearness to structures important to the arm, to prevent local recurrences; in other words, tumors that are locally malignant due to their anatomical location and not from their morphologic composition.

Most probably the more malignant lesions will continue to be treated by local excision and/or irradiation until the biologic properties of the lesion have asserted themselves and metastatic deposits preclude more than efforts at symptomatic relief. Few surgeons would have the temerity to insist on radical amputation when first confronted with such a lesion in its virgin state, and a person who would submit to such a deforming and crippling operation without first giving conservative measures a trial scarcely can be imagined. The two following case records, we believe, exemplify the types of lesions in which interscapulothoracic amputation will most frequently be of value.

### CASE REPORTS

CASE 1.—A part Hawaiian male first came under our care on Jan. 13, 1923, at the age of 31 years, complaining of a swelling in the posterior region of the left shoulder. He attributed his trouble to having been struck by a baseball in this region in 1914. However, it was not until 1918 that a swelling was first noticed in this area. This tumor was removed at that time. It recurred and was removed along with the scapula in 1919. In July, 1922, a twenty-two-pound mass was again removed from the back of the shoulder. On Feb. 7, 1923, the mass in the posterior part of the shoulder, as shown Fig. 1, and a smaller one above the clavicle were removed, and 200 mg. of radium were implanted into the wound and left for twenty-three hours.

Recurrence took place, and tumors of varying sizes about the shoulder were removed on Dec. 22, 1923, July 15, 1925, and Nov. 14, 1925. Radium was implanted into the wound on each occasion, the largest exposure being given on Nov. 14 when 200 mg. of radium were allowed to remain for forty-eight hours. All during this time the patient stoutly refused to submit to an operation that would sacrifice the arm. From the large doses of radium used, severe radium burns resulted. However, on March 29, 1926, the patient returned with a beginning gangrene of the fingers. The arm was cold and cyanotic, and the radial pulse was barely perceptible. A large recurrence had taken place in the axilla which had involved the axillary vessels. On March 31, 1926, the arm, including the clavicle, was removed, but a wide dissection of the axilla did not seem justifiable at this time because of the patient's rather poor condition. One month later, on April 26, 1926, the patient meanwhile having greatly improved, a very radical removal of the involved area was carried out. The subclavian vessels were ligated medial to the anterior scalenus muscle. The cervical nerves giving rise to the brachial plexus were severed in the same region. A



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wide circle of skin was made and carried down to include a large portion of the pectoralis major and minor muscles and the anterior edge of the trapezius muscle. A portion of the second rib that had become necrotic was removed, along with the axillary contents, well below the recurrence and down to the chest wall. The dissection was carried so high on the subclavian vein that injury to the thoracic duct took place, as evidenced by a spill of considerable chyle into the operative wound. A gauze pack was placed in the area from which chyle was seen to ooze, and, when it was removed several days later, no further discharge of this nature was seen. Following the operation an uneventful recovery took place, and no evidence of recurrence has since been noted. This individual has carried on with his work as a court stenographer and in spite of the loss of the arm and shoulder is able to hunt and shoot birds with considerable accuracy. Many details in the conduct of this case have been omitted for the sake of brevity, such as x-rays for possible metastasis, transfusions, and minor complications.

*Pathologic Findings.*—With tissue from the first conservative operation the first cut of the knife revealed the fact that the tumor was obviously a chondroma, but the preparation of sections and their interpretation presented certain obstacles. The tissue was so soft and slippery and in places so mucinous and myxoid that it was most difficult to prepare frozen sections. When blocks of tissue were dehydrated for paraffin embedding, they shrank to about one-quarter of their size. No one block of tissue looked like another, and the arrangement and architecture were most uneven. The tumor was traversed by septae that carried blood vessels; in the neighborhood of these vessels the cartilage cells were numerous, small but unequal in size, clumped together in groups, apparently growing rapidly, and crowding each other,



Fig. 2.—The photomicrograph of the chondroma was made from tissue removed at the last conservative operation and shows the large number of cartilage cells, their variation in size and shape, and their clumping together. Arrows indicate some of the mitoses, poorly shown because of technical difficulties in preparing thin sections.

though, after search, no mitoses were found in these sections. In other remote areas the cartilage cells were sparse and large. The matrix itself was quite without structure and very abundant in some areas, slightly granular in other areas, and wholly mucinous in others. It was considered myxoid rather than truly myxomatous. Subsequent conservative operations yielded tissue that did not differ microscopically from the first. On no one slide alone could a differential diagnosis between benignity or malignancy be made. However, the variation in size of cells and particularly the presence of the smaller ones with hyperchromatic nuclei inclined us toward considering the tumor as malignant. The constant recurrence of the tumor after multiple operations strengthened us in our conviction.

All subsequent sections examined were similar to the first except those from the last conservative operation before the radical one, when the tumor had become much more cellular, the cells varied more greatly in size and shape, and frequent, rather irregular mitoses appeared (Fig. 2).

In brief, no one or more slides at any time, except for those from the last conservative and final radical operation, gave absolute evidence of the malignancy of this chondroma, a group most difficult for accurate histologic diagnosis. The combination, however, of the sections and the history of recurrence made certain of the local malignancy.



Fig. 3.—Following interscapulothoracic amputation.

CASE 2.—A Caucasian male, aged 62 years, came under our observation on Dec. 1, 1937. His trouble dated back to 1904, at which time he was bitten on the top of the right shoulder by a venomous snake (Queensland death adder) in Australia. A keloid first began to develop in this area in 1912 and was excised in 1913. No further trouble was noticed until 1935 when a swelling developed in the same region for which several applications of radium were administered.

In December, 1937, examination revealed a tumor approximately 2 cm. in diameter situated midway between the clavicle and spine of the scapula on the superior aspect of the right shoulder. There was considerable breaking down of the surrounding superficial tissue, apparently the result of previous irradiation. The patient complained of much pain in the involved area. X-rays of the shoulder showed no bone involvement. A radiograph of the chest revealed no demonstrable metastasis. The first operation was performed on Dec. 7, 1937. As radical a removal of the tumor and adjacent ulcerated area was done as seemed justifiable. This included a portion of the deltoid muscle, a portion of the trapezius muscle, and areas close to the brachial vessels and anterior to the clavicle.

The pathologic report of the removed tissue was "fibrosarcoma of low malignancy." Various sections of the tissue removed from different areas of the operative specimen were described as: "(a) Pure, hard, fibrous keloid, (b) fibroma very

like uterine fibroids, and (e) fibrosarcoma with mucoid type of degeneration but many mitoses."

From this operation the patient made a good recovery. Examination of the specimens seemed to show adequate removal. The area was later successfully skin-grafted.

A second operation was performed. On July 22, 1938, at a follow-up examination, a small, freely movable nodule approximately 1.5 cm. in diameter was removed just below the outer third of the clavicle. Examination of the tissue elicited the following report: "Tissue: Recurrent fibrosarcoma. Tissue looks rather mature, ripe, and relatively benign, closely resembling keloid, but there are many mitoses present." Shortly thereafter another nodule was seen to be developing just lateral to the one described. At this point it was decided that the patient should be given the benefit of consultation, particularly as related to irradiation. He was referred to Dr. Edwin I. Bartlett, of San Francisco, whose opinion and treatment are briefly recorded as follows:

After examining the patient and reviewing the microscopic slides submitted in consultation with x-ray and pathologic chiefs at the University of California Hospital, it was decided that the situation looked serious but that surgery followed by irradiation seemed justifiable. It was felt that the lesion was a sarcoma of high local virulence but of low grade as far as metastasis was concerned.

At operation a large nodule was found attached to the clavicle, and another mass of tumor was found beneath the clavicle and adherent to it at the site of the previous operation. All the involved tissue was removed with wide margin and was packed down to the fossa behind the clavicle, so as to leave exposed the area of deepest recurrence.

A subsequent communication from Dr. Bartlett read as follows: "I warned Mr. — that we could not guarantee against a future recurrence and that time only would tell. He seemed to understand the situation thoroughly but felt as I did that after Dr. Taussig's rather strenuous treatment with radium the chances of recurrence were reduced to a minimum."

The patient returned to our care on Sept. 22, 1938. A fourth operation was performed on Oct. 5, 1938. He was again subjected to operation because of the appearance of a tumor just beneath the outer third of the clavicle. The tumor, which was approximately 2 cm. in diameter, was found lying beneath and in the pectoralis major muscle. It was attached to, but apparently not involving, the under surface of the clavicle. Due to its intimate contact with the brachial plexus and associated vessels, complete gross removal of the tumor seemed doubtful. Eight 2 mg. tubes of radium were packed into the edges of the wound and allowed to remain for forty-eight hours.

A fifth operation was performed on Dec. 14, 1938. A recurrence had taken place above the clavicle a little medial to its midportion. This could be only inadequately removed because of its adherence to the brachial vessels. Ten 1 mg. tubes of radium were implanted around the edge of the wound and allowed to remain for forty-eight hours.

*Pathologic Report.*—Tissue removed at the primary operation and the two subsequent conservative ones showed, in histologic preparations, a remarkable similarity, the same spindle-shaped cells in bands and whorls and the whole section quite homogeneous and not unduly vascular. The earlier sections contained few or no mitoses. The sections from this last conservative operation showed again a similar picture save that very many mitoses were now present, even though they were small, compact, and not outstandingly irregular (Fig. 5).

Subsequent recurrences took place in the regions previously described, and at Dr. Bartlett's suggestion these were injected with cystine hydrochloride, according to the technique as described by Dr. Jesse L. Carr. They apparently were not enthusiastic about the results to be expected but had noted some encouraging results.

One hundred milligrams of cystine hydrochloride were dissolved in 2 c.c. of freshly boiled water and injected immediately into the center of the recurrence. Seven such injections were given without apparent benefit.

Fig. 4 taken at this time shows an ulcerated area containing a recurrence above the clavicle and two prominences below the clavicle, seats of other recurrences.

At this time it was felt that all of the possibilities of conservative treatment had been exhausted and that any hope of cure lay in interscapulothoracic amputation. Repeated examinations revealed no demonstrable evidences of metastasis.

On Feb. 25, 1939, Dr. Bartlett was again appealed to, and he kindly wrote:

"We are still of the opinion that there is a sarcoma of high local virulence but of low grade as far as metastasis is concerned.

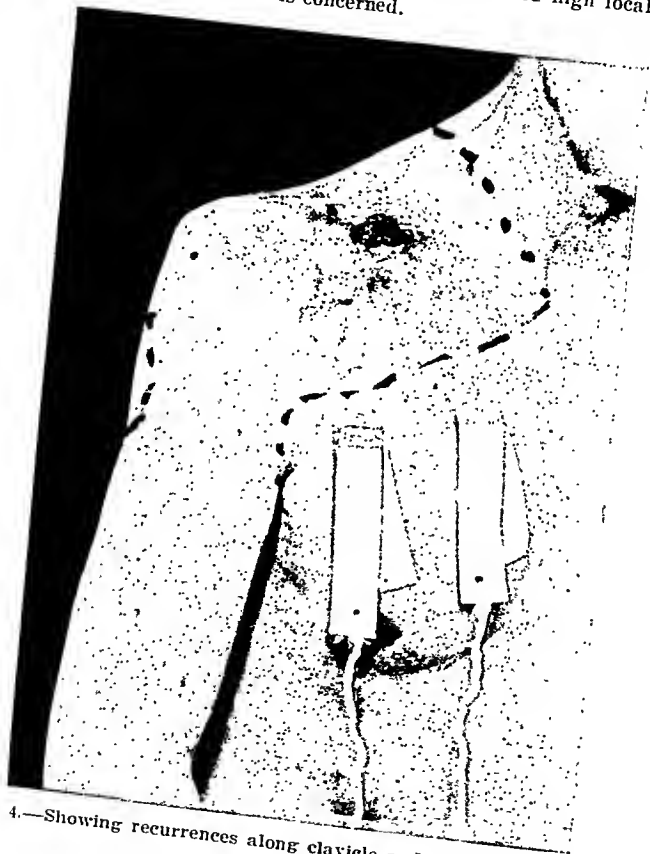


Fig. 4.—Showing recurrences along clavicle and outline of incision.

"In the event, therefore, that we can be reasonably certain that there can be no metastasis by thorough x-ray examinations we are faced with removal of the arm and shoulder girdle to save the life of a patient who is already not young, or the other alternative of continuing as in the past until such time when metastasis occurs.

"While a shoulder girdle amputation is a big piece of surgery and carries with it a certain degree of shock, I feel that Mr. — could safely embark on such a procedure. As to mutilation, there is nothing much more severe, but he can be fitted with a shoulder apparatus which will carry his clothes just as well as the real shoulder."

A sixth operation, interscapulothoracic amputation, was performed on March 7, 1939. Incision was made as shown by the tracing in Fig. 4. In order to determine

whether or not the condition was operable, the clavicle was first disarticulated at its sternal attachment and the incision carried back across the base of the neck and to the chest wall by severing the upper medial portion of the pectoralis major muscle. Opportunity was afforded by lifting the clavicle to explore the structures beneath. This maneuver was considerably handicapped as a result of much scar tissue formation from previous operative trauma and irradiation. There being no evidence of extension of the lesion to these areas, the operation was performed. The subclavian vein was ligated first; the anterior scalenus muscle was then severed after isolating and protecting the phrenic nerve; this gave adequate exposure of the subclavian artery which was then ligated. It does not seem necessary to describe in detail the

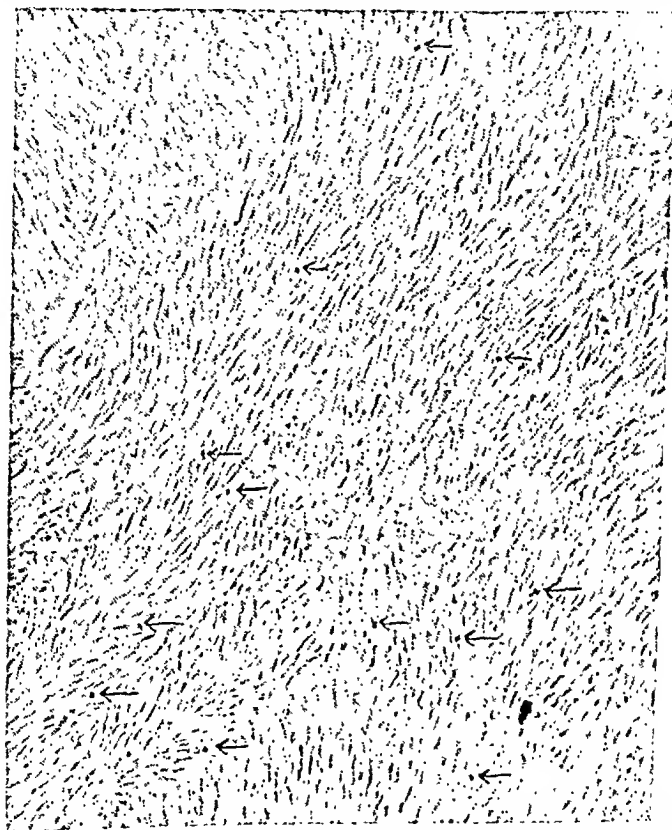


Fig. 5.—The photomicrograph of the fibrosarcoma was made from tissue removed at the last conservative operation and shows the homogeneity of its structure, the spindle cells arranged in bands and whorls, their similarity in size and shape, and the avascularity. Arrows indicate the very numerous, but rather normal, small mitoses and pyknotic nuclei.

operation of interseapulothoracic amputation since this has been adequately covered by many standard treatises on this subject. It would seem, however, that an approach such as the one described permits the control of the vascular supply to the operative field from the start and also enables one to explore the regions which, if involved, would render proceeding with the operation inadvisable. Littlewood<sup>2</sup> advocates an approach from the back. At this particular operation a rather large skin flap from the axilla and inner aspect of the arm was preserved in order to cover the large defect. The patient stood the operation well, being given a transfusion at its completion.

A somewhat complicated convalescence ensued due to the fact that the patient developed an acute cholecystitis requiring operation.

The examination of the removed specimen revealed, in addition to the involvement previously described, a nodule of tumor tissue the size of an English walnut lying directly beneath the clavicle and intimately associated with the brachial vessels. The excision lines seemed adequate. To date, the patient is well, back at his former occupation, and without evidence of recurrence.

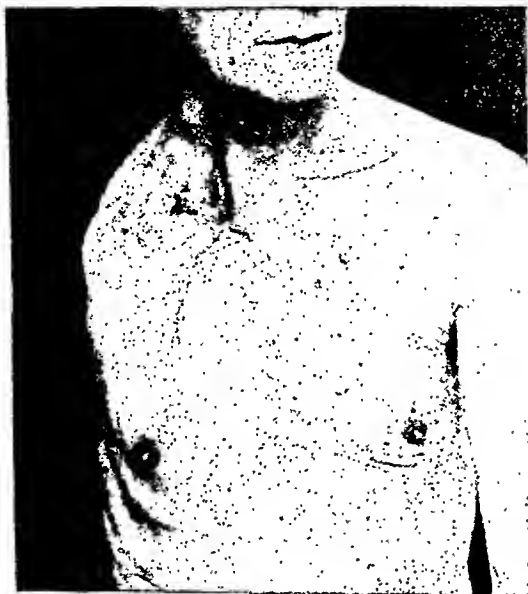


Fig. 6.—Following interscapulothoracic amputation.



Fig. 7.—Simple appliance to preserve contour of shoulder.

## SUMMARY

Two persons upon whom successful interscapulothoracic amputations have been performed are reported. They suffered from conditions which we believe most frequently justify the operation under discussion; namely, patients suffering from locally malignant and recurring tumors, not prone to metastasize, so situated that they cannot be effectively removed locally because of their close proximity to structures important to the arm.

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# METASTASES IN THE SKULL FROM CARCINOMA OF THE THYROID

## A CLINICAL AND ROENTGENOGRAPHIC STUDY OF TWO CASES WITH A BRIEF SURVEY OF THE LITERATURE

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**B**ULKY soft tissue tumors which involve the skull are not very common and when seen usually present a problem in differential diagnosis. The tendency for thyroid carcinomas to metastasize to the skull is recognized generally. However, the insidious character of the primary growth, the long latent period which often supervenes between the recognition of the primary growth and its secondary manifestations, and the unusual characteristics of the secondary tumor in the skull often make the diagnosis difficult.

### LITERATURE

The incidence of carcinoma of the thyroid, as given by different writers, varies between 0.5 and 2 per cent of all thyroid disease. Hare and Swinton<sup>1</sup> found primary malignant disease of the thyroid to be present in 2.4 per cent of the cases in a series of 15,522 thyroid operations on 12,946 patients at the Lahey Clinic. In the series of almost 17,000 thyroidectomies reported by Crile and his associates,<sup>2</sup> malignant disease was present in approximately 2 per cent. Metastases from carcinoma of the thyroid are found most frequently in the lungs. The combined figures of Pemberton,<sup>3</sup> Ehrhardt,<sup>4</sup> and Dinsmore and Hicken,<sup>5</sup> give an average incidence of 31 per cent pulmonary metastases in a total of 940 cases. In Pemberton's series of 438 cases there was metastasis to the lungs in 24 per cent, while Ehrhardt<sup>4</sup> reported metastasis to the lungs in 54 per cent of 238 cases of all types of malignant goiter. Dinsmore and Hicken<sup>5</sup> found pulmonary metastasis in 14 per cent of 264 cases.

Despite the higher frequency of pulmonary metastasis, most attention has been directed toward the skeletal system as the site of secondary growths. Carcinomas of the thyroid, along with carcinomas of the breast and prostate, have a striking tendency to metastasize to bone. The special interest in the skeletal system is due probably to the relatively high incidence of involvement and to the fact that a secondary growth in bone may be the first indication of malignant disease in the thyroid gland. Dinsmore and Hicken<sup>5</sup> were able to find in the literature

223 cases of bone metastases from malignant goiter. These writers found that 6 per cent of their 264 cases of malignant thyroid disease metastasized to bone or 18 out of 124 cases in which metastases were present. Pemberton<sup>3</sup> also found 6 per cent of his 438 cases of malignant thyroid disease had secondary growths in the skeletal system.

The predilection for secondary thyroid carcinoma to involve certain of the bones of the skeletal system has been recognized for some time. While the metastatic lesions are occasionally single, in most instances there are multiple foci with involvement of several organs or systems. According to Ewing,<sup>6</sup> the metastases generally appear first near the cranial sutures in the skull or in the region of the epiphyses in the long bones. The most frequent sites of localization within the skeletal system are the skull, vertebrae, and pelvis. Deposits are also commonly found in the sternum, mandible, femur, clavicle, and ribs. The subject has been reviewed by several writers, notably Joll,<sup>7</sup> Simpson,<sup>8</sup> and Ginsburg.<sup>9</sup>

Metastatic lesions to the skull occasionally appear as an isolated lesion, but the metastatic process is usually more widespread. Many of these metastatic lesions exhibit pulsations synchronous with the arterial pulse and may be mistaken for aneurysms. Crile<sup>10</sup> has recently reported four such lesions of the sternum and reviewed the literature upon the subject.

One of the first pulsating tumors of this sort to be reported was that of Morris.<sup>11</sup> In this case a large parietal lesion developed and later began to pulsate before multiple metastatic lesions became apparent in the skeletal system. The early literature contains several reports of bulky metastatic tumors of thyroid origin in the skull. Haward's<sup>12</sup> case had a large pulsating tumor in the skull as well as in the left scapula and iliac bone. Death in that instance was due to the cranial lesion which had reached sufficient size to cause compression of the brain. Wölfer's<sup>13</sup> case was of a rapidly growing frontal lesion which was associated with enlargement of the left lobe of the thyroid. A similar case was reported by Cramer.<sup>14</sup> Kanoky<sup>15</sup> in 1916 reported a case in which a metastatic tumor arose in the left temporal region. At death it was found that the growth was attached to the dura and had displaced fully one-third of the contents of the left side of the cranial cavity. Recently Connell<sup>16</sup> has reported two cases of massive metastatic tumor to the skull. In his first case there was no biopsy of either the primary or secondary growth and the diagnosis was made clinically. A biopsy of the cranial tumor in the second case was diagnosed as adenocarcinoma subsequent to fetal adenoma, the diagnosis of carcinoma having been made chiefly from the metastatic nature of the tumor. The growth had destroyed the outer table and most of the inner table of the occipital region of the skull. Williamson<sup>17</sup> has reported a similar case in which the skull was the site of three large growths which had destroyed much of the underlying bone. Although there was no biopsy of either the

primary or secondary growths, the thyroid gland was markedly enlarged. In both of Connell's cases there was a palpable mass in the thyroid gland. None of the cases reported by these two authors exhibited pulsation.

*Pathology.*—It is generally recognized that carcinomas of the thyroid may exhibit few histologic evidences of malignancy, either in the primary or secondary growths. Müller<sup>18</sup> in 1871 was apparently the first to note the tendency for metastatic lesions of the thyroid to appear microscopically benign. The much quoted case of Cohnheim<sup>19</sup> in which a "benign adenoma" of the thyroid metastasized to bone has been reviewed by several writers<sup>5, 8</sup> and it is generally agreed that the tumor in question showed definite evidence of malignancy. The concept that "benign adenomas" of the thyroid can give rise to distant and widespread metastases has gained favor with some writers. Joll<sup>7</sup> accepted this view and collected from the literature forty-three cases in which bone metastases were associated with a "normal thyroid or benign goiter" and added another of his own. Kanoky,<sup>15</sup> in reviewing the literature from the standpoint of nonpulsating tumors of the skull, also accepted this concept. Similarly, Ginsburg,<sup>9</sup> in a study of bone metastases in thyroid tumors, concluded: "Bone metastasis is of frequent occurrence not only in carcinoma and sarcoma but also in simple adenoma of the thyroid gland."

Many writers, however, especially those who have studied the problem more recently, do not accept such an entity as the benign metastasizing adenoma or goiter. Simpson<sup>8</sup> carefully reviewed the literature and came to the conclusion that there is no "benign metastasizing goiter." Similarly, Dinsmore and Hicken<sup>5</sup> were led to conclude that the so-called benign metastasizing adenomas are malignant lesions and agree with Simpson that the term is misleading and should be abandoned. Graham<sup>20, 21</sup> emphasizes the careful study of the tumor for local evidence of malignancy and states that in his cases in every instance in which metastasis has occurred from a malignant adenoma blood vessel invasion has been noted. In a study of four cases of malignant adenoma of the thyroid with local recurrences in the veins of the neck, Graham<sup>22</sup> states: "In none of the cases was the tumor as a whole frankly carcinomatous from a purely histological standpoint. . . . The pathologist as well as the clinician at the time of the primary operation had difficulty in making a positive diagnosis of malignancy." On this basis Crile and Crile, Jr.,<sup>23</sup> have advocated radical resection of the neck veins in cases of malignant tumors of the thyroid gland.

#### REPORT OF CASES

CASE 1.—A 41-year-old white woman was first admitted to the hospital in February, 1931, with the complaints of enlargement of the right side of the neck and a swelling on the head. In the spring of 1930 she had first noticed a hard, painless lump in the right side of the neck. The following summer the patient

developed a painless swelling in the left frontoparietal region, which gradually increased in size, but the patient did not consult a doctor until about ten months previous to hospital admission. The past history was essentially noncontributory. There had been no cranial trauma, night sweats, palpitation, or weight loss.

The positive physical findings at the time of admission were limited essentially to the head and neck. The right lobe of the thyroid was considerably enlarged. The portion of the lobe which was adjacent to the trachea was of stony hardness and fixed to the contiguous structures, while the remaining tissue was soft and diffusely enlarged. The gland did not pulsate and no bruit could be heard. Laryngoscopic examination revealed a normal larynx with no evidence of vocal cord paralysis.

In the left frontoparietal region was a pulsating tumor which measured 4 by 1.5 cm. The mass was fixed to the underlying structures and, although the pulsations were synchronous with the heart beat, no bruit could be heard. Neurologic examination gave normal results. The basal metabolic rate was plus 10 per cent.

Stereoroentgenograms of the skull showed an area of bone rarefaction in the left frontoparietal region which measured 4.5 by 4 cm. (Fig. 1). Films taken with the rays tangential to this area demonstrated a thinning of both tables of the skull with a suggestion of radiating bony spicules. The defect had slightly irregular borders but was fairly sharp in definition. The surrounding bone was the seat of slight sclerosis.

The clinical diagnosis was carcinoma of the thyroid with metastasis to the skull. A right thyroid lobectomy was performed from which the patient made an uneventful recovery.

Following operation the patient received x-ray therapy to the tumor mass in the skull. During the succeeding nine months the size of the growth increased to 6 by 7 by 2 cm. It was tender at the base, firm, but not hard and was fixed to the skull but not to the overlying skin. Auscultation revealed no bruit and it had ceased to pulsate. Neurologic examination was normal and the only complaint at the time was that of severe headache. Roentgenograms of the skull at this time showed marked increase in the extent of bone destruction (Fig. 2). The defect measured 8 by 4.5 cm. and the involved bone appeared to have been almost completely destroyed. There was involvement of the temporal region which had not been seen on the previous films. The bone adjacent to the area involved by the tumor showed a more marked sclerosis than previously. There was no evidence of increased intracranial pressure.

At operation the tumor was found to have penetrated the skull and become adherent to the underlying dura. The tumor surrounding calvarium and upper leaf of the attached dura were removed. The patient made an uneventful recovery and was discharged from the hospital on the thirteenth postoperative day.

One year later the complaint of abdominal pain led to the discovery of an enlarged and tender liver. Subsequent examinations revealed progressive nodular enlargement of the liver. Her course was progressively downhill; she lost weight, developed a marked anemia, and became cachectic. At her last visit, three years after removal of the metastatic lesion in the skull, there was a nodule 2 cm. in diameter at the posteroinferior margin of the temporal bone defect. There were a number of enlarged and firm lymph nodes in the cervical chain. The patient died in December, 1934. Autopsy was not obtained.

*Pathology.*—The right lobe of the thyroid removed at operation measured 8 by 8 by 4 cm. While the greater portion of the gland was composed of firm yellow-brown tissue, the upper pole contained a circumscribed nodule 4 cm. in diameter. This nodule contained cartilage and bone, while several small adjacent nodules appeared to be composed of normal thyroid tissue. The capsule of the gland was everywhere intact.

Microscopically, the greater portion of the lobe consisted of clusters and cords of cells of variable size, shape, and staining qualities. In some areas there were cystic spaces filled with colloid. Many dilated capillaries were present between the cell clusters and some of these showed evidence of invasion by the adjacent tumor tissue. Invasion of the fibrous trabeculae which formed part of the stroma of the

Fig. 1.



Fig. 2.

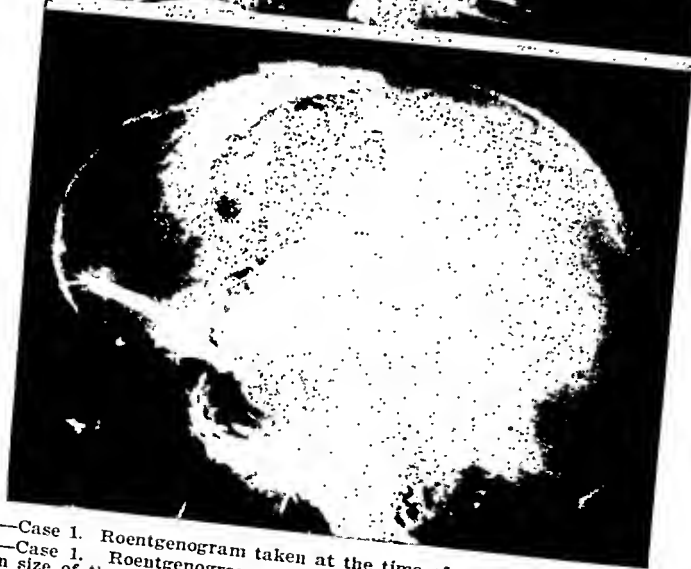


Fig. 1.—Case 1. Roentgenogram taken at the time of admission.

Fig. 2.—Case 1. Roentgenogram taken about nine months after admission. Note increase in size of the defect despite local x-ray therapy.

growth was also present in many places. The large nodule at the upper pole of the lobe was composed of dense fibrous tissue, acini filled with colloid, and foci of calcification. Sections through the smaller nodules revealed normal thyroid tissue. The pathologic diagnosis was carcinoma of the thyroid gland.

The tumor with adjacent calvarium removed from the parietal region of the skull measured 9 by 8 by 5.5 cm. Grossly, the tumor tissue had an opaque, yellow appearance and contained many large, intercommunicating cysts filled with transparent,

mucilaginous material which resembled colloid. (Fig. 3.) There was complete destruction of the involved calvarium aside from a few small fragments of bone within the tumor. The growth, which projected about 2 cm. into the cranial cavity, was firmly adherent to the outer leaf of the dura.

Fig. 3.

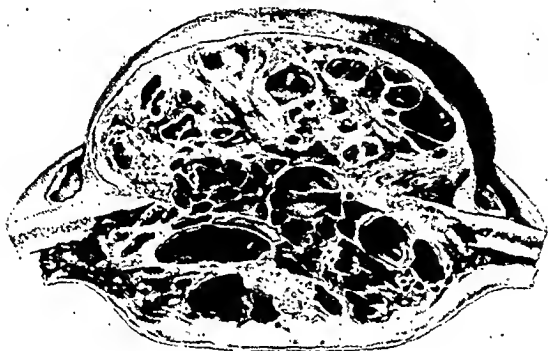


Fig. 4.

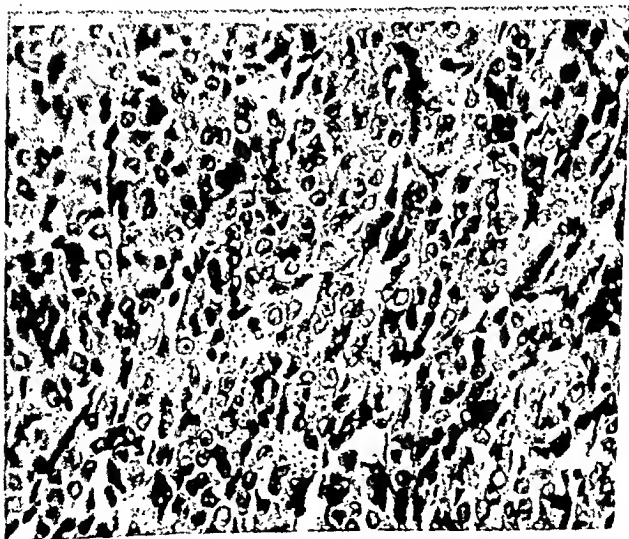


Fig. 3.—Case 1. Drawing of the specimen removed at operation. The specimen includes the tumor, adjacent calvarium, and outer leaf of the dura to which the growth is adherent.

Fig. 4.—Case 1. Photomicrograph of the more cellular portion of the tumor in the calvarium. Note the cell cords separated by thin strands of connective tissue. (Hematoxylin and eosin, X250, green filter.)

Microscopically, the tumor was very cellular, being composed of cells with large, round, pale nuclei and vacuolated cytoplasm with indistinct cytoplasmic outlines. The cells lay in a loose connective tissue stroma and showed a distinct tendency toward acini formation. Many of the acini were dilated and filled with colloid. The latter was present as well in the reticular stroma of the tumor. There was no histologic evidence of invasion of either the periosteum or dura,

although tumor thrombi could be observed in many of the smaller vessels. Only an occasional mitotic figure was observed. The pathologic diagnosis was metastatic carcinoma of the thyroid in the calvarium. (Fig. 4.)

The clinical diagnosis in this case was fairly obvious since both primary and metastatic lesions were demonstrable. A two-year interval between the first and subsequent metastases and a three-and-one-half-year survival following the appearance of the first metastatic lesion suggests that the tumor was not highly malignant. It is significant that symptoms of cerebral compression were absent despite the rapid growth of the metastatic lesion and the large size it had attained at the time of removal. Although the growth had become adherent to the dura, the latter proved to be rather resistant to invasion by the tumor.



Fig. 5.—Case 2. Photograph of the tumor which presented over the left parietal and occipital region but involved the right side as well.

CASE 2.—A 50-year-old white woman was first seen in September, 1934, with the complaint of a swelling on the back of the head of eight years' duration. About eight years previously she had been struck over the left parietal region with a heavy brass curtain rod. She was not unconscious and had no subsequent symptoms other than a slight "dent" and slight tenderness in this region. During the following year there slowly developed a small tumor about 1 to 2 cm. in diameter at the site of the trauma. Although the tumor had slowly increased in size during the first three years, in the following three years it had doubled in size. In June, 1934, the patient suffered several episodes of hematuria associated with pain which began in the left costovertebral angle and radiated anteriorly.

At the age of 14 years the patient had a goiter. This reappeared with each of her subsequent four pregnancies but had also subsided during the puerperium.

However, following the last pregnancy the enlargement persisted and was removed by a right thyroid lobectomy in 1921.

Examination revealed a large, pulsating, soft tumor over the posterior parietal and occipital region. This involved the entire left side but extended beyond the midline to include the right as well (Fig. 5). The pulsations were synchronous with the radial pulse and a soft bruit could be heard. The tumor was firmly attached to the underlying calvarium but did not appear to involve the scalp. There was visible distention of the superficial temporal and angular veins on both sides of the head. Neurologic examination gave normal results.

Roentgenograms of the skull at various stages in the development of the tumor were available. Films taken in June, 1929, about three years after the local injury, disclosed a destructive lesion in the left parietooccipital region which measured about 5.5 by 3 cm. (Fig. 6). The defect was irregular in outline but moderately well demarcated. Anteroposterior views of this region disclosed the lesion to consist of marked rarefaction of both tables of the calvarium with almost complete destruction of the bone in some areas. The region involved by the growth as well as the rest of the skull showed accentuation of the vascular markings.

Films taken in August, 1934, showed marked extension of the lesion to form a defect without evidence of osseous structure which involved the entire left occipitoparietal region and extended beyond the midline to the right (Fig. 7). At this time it measured 8 by 10 cm. in its two greatest diameters. The contour of the defect was rather irregular, but the adjacent bone showed no unusual characteristics. In this region and throughout the skull the vascular markings were very prominent. There was no demonstrable intracranial calcification and no evidence of increased intracranial pressure.

The impression was a metastatic malignant tumor of the skull, although the possibility that the growth might be either a meningioma or a vascular tumor of the skull was also considered. The patient entered the hospital in March, 1935, for further study. At this time the growth measured about 12 by 10 cm.

Further investigation of the previous thyroidectomy disclosed that the tissue removed at that time was regarded microscopically as a fetal adenoma. Repeat films of the skull on admission disclosed but little enlargement of the destructive process as compared with the size of the lesion in August, 1934. The borders of the defect were quite irregular and showed moderate sclerosis. Roentgenograms of the pelvis revealed a large destructive lesion in the right iliac wing with involvement of the inferior segments of the coccyx and entire sacrum. The clinical diagnosis was carcinoma of the thyroid with metastasis to the skull, pelvis, coccyx, and kidneys.

It was decided to remove the growth from the skull. At operation the tumor proved to be exceedingly vascular and after reflecting the scalp and encircling the bone adjacent to the tumor the remainder of the procedure was postponed for another session. At the second operation the tumor was found to have a wide attachment to the underlying dura. During the process of elevating the bone flap, this pedicle was broken across and the ensuing hemorrhage could not be controlled. In spite of a transfusion of 2,000 c.c. of blood the patient expired.

*Pathology.*—The tumor with several small pieces of calvarium removed at operation weighed 458 Gm. after fixation in 10 per cent formalin. The growth itself measured 12.5 by 10 by 6.5 cm. and had a fleshy consistency with the gross characteristics of normal thyroid tissue. The rim of calvarium about the tumor showed obvious invasion by the neoplastic tissue.

At autopsy, only a small portion of the right lobe of the thyroid was present. This was uniformly light pink in color and, although it was closely adherent to the

trachea, there was no gross evidence of invasion. The left lobe of the gland appeared normal. The positive autopsy findings were limited to the brain, pelvis, and kidneys. At the site of the operative wound there was a pedunculated mass of tumor tissue adherent to the dura. This measured 5 cm. in diameter and had a

Fig. 6.

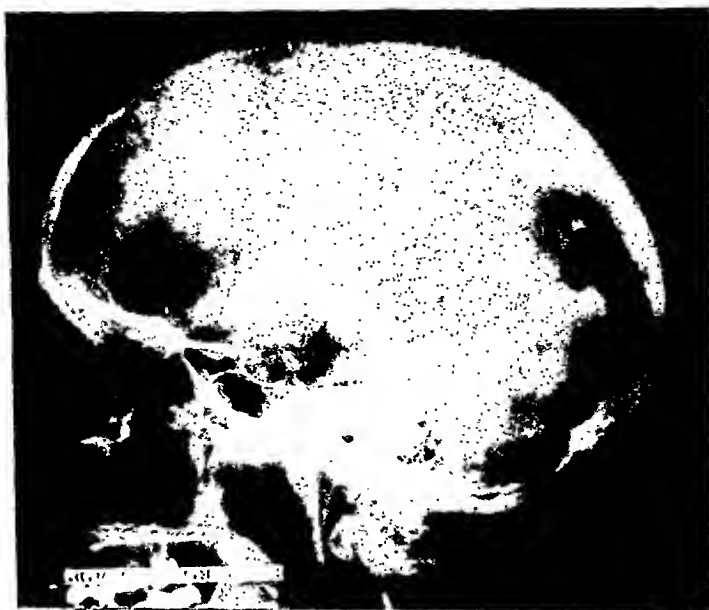


Fig. 7.



Fig. 6.—Case 2. Roentgenogram taken about three years after the local injury and about five years before admission.

Fig. 7.—Case 2. Roentgenogram taken about five years after that shown in Fig. 6 and at the same time as that shown in Fig. 5. Note the widespread involvement and the complete destruction of both tables of the skull.

However, following the last pregnancy the enlargement persisted and was removed by a right thyroid lobectomy in 1921.

Examination revealed a large, pulsating, soft tumor over the posterior parietal and occipital region. This involved the entire left side but extended beyond the midline to include the right as well (Fig. 5). The pulsations were synchronous with the radial pulse and a soft bruit could be heard. The tumor was firmly attached to the underlying calvarium but did not appear to involve the scalp. There was visible distention of the superficial temporal and angular veins on both sides of the head. Neurologic examination gave normal results.

Roentgenograms of the skull at various stages in the development of the tumor were available. Films taken in June, 1929, about three years after the local injury, disclosed a destructive lesion in the left parietooccipital region which measured about 5.5 by 3 cm. (Fig. 6). The defect was irregular in outline but moderately well demarcated. Anteroposterior views of this region disclosed the lesion to consist of marked rarefaction of both tables of the calvarium with almost complete destruction of the bone in some areas. The region involved by the growth as well as the rest of the skull showed accentuation of the vascular markings.

Films taken in August, 1934, showed marked extension of the lesion to form a defect without evidence of osseous structure which involved the entire left occipitoparietal region and extended beyond the midline to the right (Fig. 7). At this time it measured 8 by 10 cm. in its two greatest diameters. The contour of the defect was rather irregular, but the adjacent bone showed no unusual characteristics. In this region and throughout the skull the vascular markings were very prominent. There was no demonstrable intracranial calcification and no evidence of increased intracranial pressure.

The impression was a metastatic malignant tumor of the skull, although the possibility that the growth might be either a meningioma or a vascular tumor of the skull was also considered. The patient entered the hospital in March, 1935, for further study. At this time the growth measured about 12 by 10 cm.

Further investigation of the previous thyroidectomy disclosed that the tissue removed at that time was regarded microscopically as a fetal adenoma. Repeat films of the skull on admission disclosed but little enlargement of the destructive process as compared with the size of the lesion in August, 1934. The borders of the defect were quite irregular and showed moderate sclerosis. Roentgenograms of the pelvis revealed a large destructive lesion in the right iliac wing with involvement of the inferior segments of the coccyx and entire sacrum. The clinical diagnosis was carcinoma of the thyroid with metastasis to the skull, pelvis, coccyx, and kidneys.

It was decided to remove the growth from the skull. At operation the tumor proved to be exceedingly vascular and after reflecting the scalp and encircling the bone adjacent to the tumor the remainder of the procedure was postponed for another session. At the second operation the tumor was found to have a wide attachment to the underlying dura. During the process of elevating the bone flap, this pedicle was broken across and the ensuing hemorrhage could not be controlled. In spite of a transfusion of 2,000 c.c. of blood the patient expired.

*Pathology.*—The tumor with several small pieces of calvarium removed at operation weighed 458 Gm. after fixation in 10 per cent formalin. The growth itself measured 12.5 by 10 by 6.5 cm. and had a fleshy consistency with the gross characteristics of normal thyroid tissue. The rim of calvarium about the tumor showed obvious invasion by the neoplastic tissue.

At autopsy, only a small portion of the right lobe of the thyroid was present. This was uniformly light pink in color and, although it was closely adherent to the

## DISCUSSION

Grossly and roentgenologically the lesions in both cases presented many similar characteristics. Both lesions were destructive from the onset and gave rise to minimal peripheral bone reaction in the later stages of the process. This bone reaction was more pronounced in the second case where the destructive lesion had progressed to a more advanced stage. Both lesions were highly vascular as evidenced in the roentgenograms by the accentuated vascular markings about the lesion as well as throughout the remainder of the skull. This increased vascularity was largely venous, being due for the most part to the greatly enlarged sinuses. The enlargement of the angular and superficial temporal vessels and the necessity of a two-stage procedure in the second case demonstrates the associated vascularity of the overlying soft tissues.

Although there are several types of primary growths which produce destruction of the calvarium, only a few need be considered here. Meningiomas in some instances may cause local erosion of bone and proliferation of the adjacent bony structures, but the destruction of osseous tissue is rarely very great. The defect in the skull is usually quite irregular and associated with local increase in vascularity. Rarely perforation of the skull may give rise to large soft tissue tumors. An unusual case of this type was described recently by Davidoff.<sup>24</sup>

The hemangiomas of bone have been studied by Bucy and Capp.<sup>25</sup> A high percentage of these tumors involve either the vertebrae or the skull. The tumor may be present as a bony, hard, elevated area or there may be a central portion which is soft and pulsating. The characteristic x-ray appearance is the presence of large "sunburst" trabeculations and spicules radiating out from the plane of the bone. The cortex of the bone is frequently destroyed, but the periosteum remains unbroken, though it may be greatly expanded.

Osteogenic sarcomas are not common lesions in the skull and are characterized by destruction of bone, invasion of periosteum and soft tissues and often by the presence of radiating spicules of bone. These tumors are rapidly growing and even in the early stages there is definite loss of bone by x-ray. According to Dyke,<sup>26</sup> primary sarcoma of the skull closely simulates the bone reaction produced by meningiomas but shows more bone destruction and less vascularity.

The writers are indebted to Dr. A. W. Oughterson for permission to use his records, to Dr. Hugh Wilson for the roentgenograms, and to Dr. Harry Zimmerman for the use of the pathologic material.

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gross appearance identical with that of the tumor described above. The calvarium at the operative site measured 1 cm. in thickness. Although there was no intradural extension of the tumor, there was marked compression of the left occipital lobe of the brain with definite cerebellar herniation.

Both kidneys were the site of multiple tumor nodules, the largest of which measured 5 cm. in diameter. These nodules were fairly firm, had a light pink color and a smooth, collagenous-appearing cut surface. Tumor tissue of the same character was present in the bones of the pelvis and a mass about 4 cm. in diameter involved the coccyx.

Microscopically the tumor removed from the calvarium varied little from that of normal thyroid tissue. It was composed of acini which showed moderate variation in size and type of epithelial lining. The larger acini were lined by flattened epithelium and contained an abundance of grayish pink staining colloid. Some of the smaller acini had no content and were lined by high cuboidal or columnar epithelium. There was no interacinar colloid, no lymphocytic infiltration, and nowhere did the epithelium present more than a single layer of cells. No mitotic figures were observed. There was invasion of the adjacent calvarium and dura. Occasional foci of new bone formation were present.

The microscopic appearance of the small nodule of thyroid tissue remaining from the previous lobectomy was essentially as above. Mitotic figures were not observed and there was no invasion of the trachea.

The tumor in the kidneys closely resembled thyroid tissue of the fetal type. The majority of the acini were small and contained no colloid although some had a moderate amount of colloid and appeared not unlike normal thyroid tissue. There were no mitotic figures and no epithelial infoldings. There was some tendency toward a radial arrangement of acini about blood vessels which were numerous and large. The growths were fairly well circumscribed and compressed the adjacent renal tissue.

Microscopically, the tumor in the coccyx showed invasion of the spongy bone and complete filling of the marrow spaces. In many places the tissue was comparable to that in the kidneys, but in other places there was more obvious evidence of malignancy. In these latter areas there was little tendency toward the formation of acini and colloid material was seen lying loose in the intercellular tissues. The cells appeared less differentiated and of the more rapidly growing type. The final diagnosis was carcinoma of the thyroid with metastases to the kidneys, bones of the skull, pelvis, and coccyx.

The five-year interval between the thyroidectomy and the first indication of a metastatic lesion serve to emphasize the insidious character of malignant disease of the thyroid gland. Despite the fact that at autopsy the left lobe of the thyroid and the remaining remnant of the right lobe showed little histologic evidence of malignancy, the several metastatic lesions showed considerable variation in microscopic pictures. Thus, the tumor tissue invading the pelvis and coccyx had all the characteristics of carcinoma while that in the calvarium resembled normal thyroid. Metastatic lesions from a malignant thyroid, particularly those arising from a "malignant adenoma," may show either more or less histologic evidence of malignancy than does the primary growth. Thus, despite the histologic character of the tissue, the ability to give rise to distant metastases and the destructive and invasive character of these brands the primary growth as carcinoma.

## URINARY STONES

### A STUDY OF THEIR ETIOLOGY IN SMALL CHILDREN IN SYRIA

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**C**ALCULOUS DISEASE is now understood to be a symptom rather than a disease entity. Some factors in the causation of stones are known, but there are still many cases in which the etiology is obscure. Confusion arises from the grouping together of cases which really belong in separate classes. One group of cases should be of special interest because of the absence of common known factors; viz., young children with bladder stones, with no obstruction, no foreign body, and no known infection. This condition is not uncommon in the southern countries of Asia.<sup>2, 9, 14, 20</sup> It was common in children in Europe during the early part of the last century. It seems that there has been some change in the mode of life which has reduced the incidence.<sup>7, 9</sup> Perhaps this change is now taking place in the Orient. Does not this situation present ideal conditions for the study of the human stone problem in its simplest form? The relatively short life histories of these patients should reduce the possibilities of error with respect to etiological factors.

This paper will summarize an investigation at the American Presbyterian Hospital, Tripoli, Republic of Lebanon, Syria, during the years 1931 to 1934.

*Age.*—The occurrence of solitary bladder stones during the first few years of life seems to indicate that these cases represent a disease which begins in infancy or very early childhood (Table I). Children come to operation for bladder stones many months or years after the onset of symptoms. At the time of operation the patient has probably long since recovered from the condition which caused the stone. Recurrences are rare.

*Sex.*—All the literature points to the relative infrequency of bladder calculi in girls. The series of 41 cases in Syria consisted of 39 boys and 2 girls. The obvious explanation is that the female urethra is larger and more patulous and passes stones more easily. It seems probable that many are passed silently in both sexes.<sup>10</sup> Stone formation may be equal in the two sexes, but the patients that come for treatment are nearly all male.

*Climate.*—The aridity of the climate offers a plausible explanation; perspiration is profuse and thirst may be unduly prolonged. It has been suggested that the present geographical distribution of bladder calculi in children corresponds roughly to those areas where the camel

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family history of stone can sometimes be elicited, but it should be remembered that in these old countries the family environment is usually unchanged from generation to generation.

Cases have been reported of stones in small children associated with congenital obstruction of the bladder outlet, with congenital atony, and with diverticula. Our cases do not fall into this category; simple removal of the stone effected cure.

The cystine diathesis<sup>4</sup> is certainly an hereditary condition, but none of our cases had cystine calculi. Some writers have assumed that a so-called uric acid diathesis is responsible in some cases, but we do not know of any definite proof.<sup>18</sup>

Heredity does not seem to be an important factor in the etiology of bladder stones in children, except in cases of congenital anomaly and in the cystine diathesis.

*Endocrinopathy.*—The stones of hyperparathyroidism are composed of calcium phosphate.<sup>1</sup> In our experience most bladder stones from children are composed of uric acid (Table III).

*Infection.*—The relative absence of pyuria is a striking feature of the condition we are studying. Immediate closure of the bladder wound after removal of the stone has been reported by many surgeons in various countries.<sup>2, 12, 15, 18, 20</sup> This would not be advisable in the presence of infection. However, it is possible that infection may play an important role in the causation of stone without there being infected urine at the time of operation.

Bilharzia is not found in the areas studied.

Rosenow and Meisser reported the production of urinary calculi by placing streptococci from lithiasis patients in devitalized teeth of dogs.<sup>17</sup> Many of our cases had carious teeth, but our records are not complete enough to compare the incidence with that of the general population.

The various urea-splitting bacteria<sup>5</sup> were not considered seriously as possible causes, because most of the stones analyzed had uric acid centers (Table III).

Five of thirteen cases had definite histories of respiratory infections; in one the onset of bladder symptoms was with an acute common cold, complicated by diarrhea. Three other cases had diarrhea, which may have been secondary to the stone. Many physicians in Syria are of the opinion that calculi are the result of urinary tract infections with bacteria of the colon bacillus group. Bacillary dysentery is indeed a prevalent disease and dysuria is a common symptom during the acute phase of dysentery. Large clumps of pus and shreds of fibrin may be found in the urine of infants suffering with bacillary dysentery. However, there is no correlation of observations. We were unable to obtain a history of dysentery in most of our cases.

TABLE I\*

AGES OF 41 CHILDREN OPERATED UPON FOR BLADDER STONE IN SYRIA

AGE	NO. OF CASES	
1	4	Three-fourths of cases during the first seven years of life
2	5	
3	5	
4	6	
5	5	
6	5	
7	0	
8	3	
9	3	
10	1	
11	1	
12	1	
13	1	
14	1	
Total	41	

\*This table includes our cases and those of Ellis Herndon Hudson, formerly of Deir ez Zore, Syria; Waheeb Nini, of Tripoli, Syria; and Ernest Wyder, of Nazareth, Palestine.

is used as a beast of burden. In our cases the onset of symptoms was more often in the dry hot months of spring and summer (Table II).

TABLE II

SEASON OF ONSET OF STONE SYMPTOMS IN 14 CHILDREN IN SYRIA

MONTH	NO. OF CASES	
January	1	Two-thirds of cases during four bright hot months of spring and summer
February	0	
March	1	
April	2	
May	2	
June	2	
July	3	
August	1	
September	0	
October	1	
November	1	
December	0	

However, study of individual cases did not indicate that stone formation was the result of dehydration. Furthermore, this theory does not fully explain why stones were more frequent in Europe a century ago.

The distribution of our cases corresponds roughly to the area from which all of our hospital patients came; in other words, along the Mediterranean coast, in the Lebanon Mountain villages, in the inland cities along the Orontes River, on the agricultural plateaus, and in the desert. There is nothing to indicate that any part of Syria is exempt.

*Heredity.*—The various race groups of this part of Syria are all represented in our small series. There were no Europeans or Americans with lithiasis, but these are a very small part of the population. A

ferrescence when heated gently with dilute hydrochloric acid. No typical oxalate stones were found.

*Vitamin Deficiency.*—Osborne, Mendel, and Perry<sup>16</sup> reported that rats fed on a balanced ration without fat-soluble vitamin developed phosphatic urinary calculi. When butter is substituted for lard in the experiments, stones do not form. McCarrison<sup>13, 14</sup> made extensive similar observations, using the diet of various sections of India in his experiments.

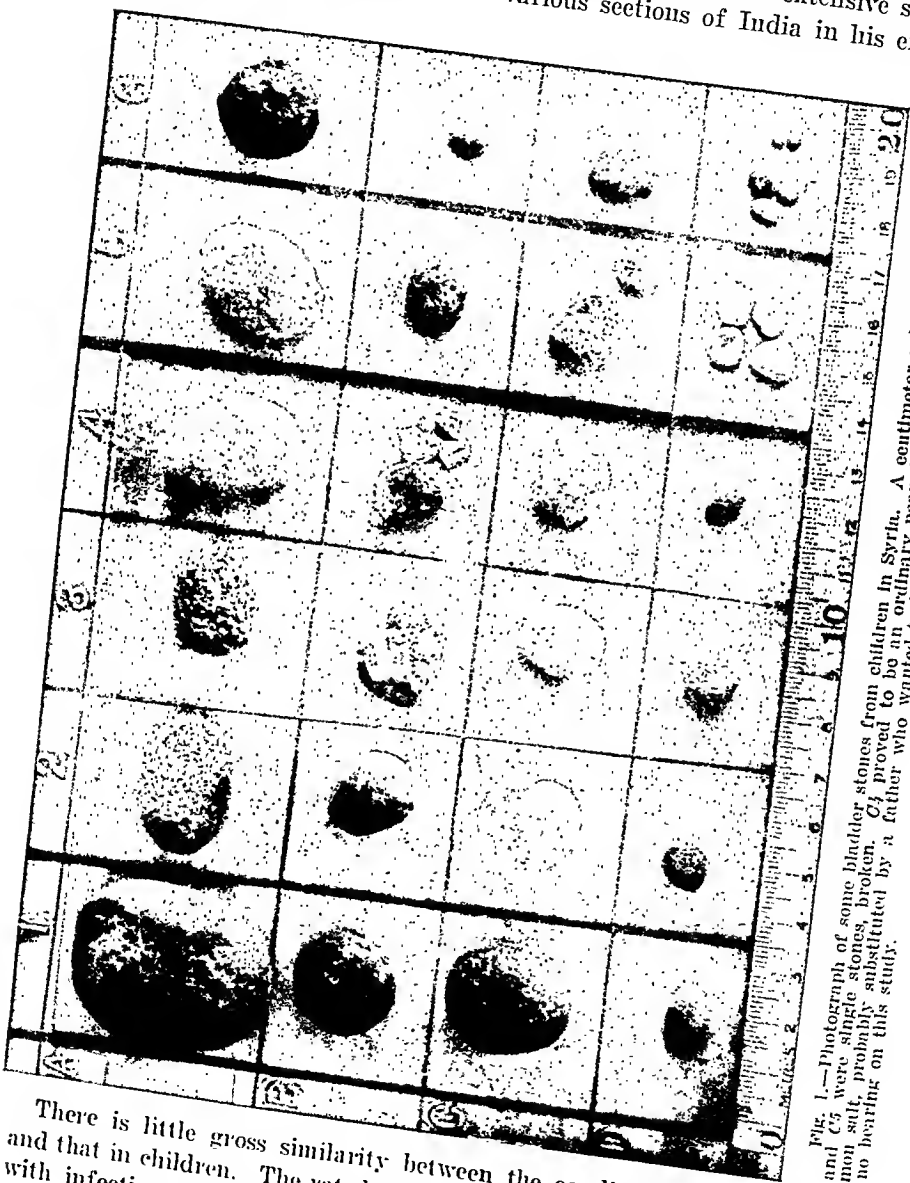


Fig. 1.—Photograph of some bladder stones from children in Syria. A centimeter rule shows the size. *B1* and *C5* were single stones broken. *C3* proved to be an ordinary peanut with a shell encrusted with common salt, probably substituted by a father who wanted to keep his son's stone. *D5* and *D6* probably have no bearing on this study.

There is little gross similarity between the condition found in rats and that in children. The rats have literally scores of phosphatic stones with infection.<sup>7</sup> Children have solitary stones, without gross evidence

TABLE III

CHEMICAL ANALYSES OF STONES PICTURED IN FIGS. 1 AND 2\*

DESIGNATION	NUCLEUS	SHELL
A 1	Uric acid-Ca and Mg phosphate	Uric acid-Ca carbonate
2	Uric acid	
3	fibrin-Ca and Mg phosphate	
4	Uric acid	Uric acid-Ca carbonate
5	Uric acid	Uric acid
6	Uric acid	Uric acid
B 1	Uric acid	Uric acid
2	Ca carbonate	Uric acid-Ca carbonate
3	Uric acid	Uric acid-Ca and Mg phosphate
4	Uric acid	Uric acid-Fibrin
5	Uric acid	Uric acid
6	Uric acid	Uric acid
C 1	Uric acid	Uric acid
2	Ca and Mg phosphate	
3	Trace uric acid	
4		
5	Ca and Mg phosphate	
6	Uric acid-Ca and Mg phosphate	
D 1	Ca and Mg phosphate	
2	Ca and Mg phosphate	
3	Ca and Mg phosphate	
4	Uric acid	
5	Uric acid	
6	Uric acid	

\*Qualitative methods of analysis were used, following the "schema of Heller."<sup>6</sup>

Leucocytosis increases the amount of uric acid excretion. Uric acid stones are frequent in cases of chronic myelogenous leucemia.<sup>21</sup> Is it possible that the leucocytosis of respiratory infections is a contributing factor in the production of uric acid calculi?

*Diet.*—Most of the substances that make up the bulk of urinary calculi are influenced by diet.

In Syria this disease is not confined to the poor, for we know of several cases in families that, according to local standards, were considered rich.

It is still a common belief that hardness of drinking water predisposes to stone formation; but stones are quite rare in some districts where the water is very hard and occur where rain water is used for drinking. There seems to be no good reason to implicate the minerals in drinking water and not the plant minerals that are ingested. The fact that the centers of many of these stones are composed of uric acid indicates that the minerals ingested have no direct influence.

Uric acid excretion in the urine ordinarily depends to a large extent upon the nucleoproteins of the diet. Syrian peasants may have no meat to eat for long periods of time, and when they do have meat the whole family usually overeats.

Oxalates were not found in any of the stones analyzed. It is possible that oxalates were present, but not in sufficient quantities to cause ef-

tion of the urinary epithelium after ten weeks of vitamin A privation, at the same period during which urinary infections and stones occur.<sup>7</sup> In other words, the mucosa is changed to skin or becomes skinlike.

The crusts which sometimes form on the skin about urinary fistulas, and preputial calculi are interesting in this connection. The question naturally arises as to whether these accretions are due to the skin surface tension alone or to the bacterial flora of the skin.

We attempted to develop a technique for the study of the morphology of the nuclei of these solitary bladder stones, searching especially for keratinized epithelium. Scrapings from the hand were mixed with pure uric acid; smears were made and studied with various stains, none of which proved satisfactory. Never could any epithelial elements be identified in the smears that were known to contain epithelium. Repeated smears from the nuclei of the stones showed nothing, except upon one occasion when three of twelve smears from different stone centers, stained at the same time with Gram's stain and decolorized with analine (two parts) and xylol (one part), showed elements which resembled epithelial cells. These may have been artefacts, but it is rather striking that they all appeared in the same staining batch. The photomicrographs were not retouched. (Figs. 3, 4, and 5).

Evaluation of a dietary with respect to vitamin A is difficult, and the conclusions may be considered conjectural.<sup>8</sup> Nevertheless, a study of the foods available in a typical Syrian market during a period of one year seemed to show that the diet was lacking in vitamin A content except for the green vegetables and fruits, and these were available during only part of the year.

Dairy products, which are ordinarily rich sources of vitamin A, are scarce and probably have a very low vitamin A content in Syria. The cows live on dry fodder for a considerable part of the year. Milk and cream are white, not yellow. All the milk is boiled immediately after milking and again before use. Butter is not used as such, but it is heated to high temperature to "clear" it, very much as lard is rendered. It seems probable that the milk has a small vitamin A content due to the poor diet of the cows and goats and that this small amount is destroyed by boiling the milk and by rendering the butter at high temperatures. By the use of the chemical color test for vitamin A, none could be detected in ordinary samples of native butter. Adding commercial vitamin A concentrate to boiling butter makes the color test become strongly positive, but it becomes negative again with a few minutes' boiling.

The seasons during which the fresh foods are available differ in various parts of the country, but transportation of garden stuffs has not been developed to any great extent. The existence of some seasonal dietary insufficiency might be suggested by the voracious ap-

of infection. However, the prime causative factor may not be related to the substance that makes up the bulk of the concretion. It should be remembered that most mammals excrete allantoin instead of uric acid; man, the anthropoid ape, and the Dalmatian coach hound are exceptions to this rule. Uric acid stones are not found in animals,<sup>9</sup> except in experimental animals with Eek fistulas.<sup>5</sup>

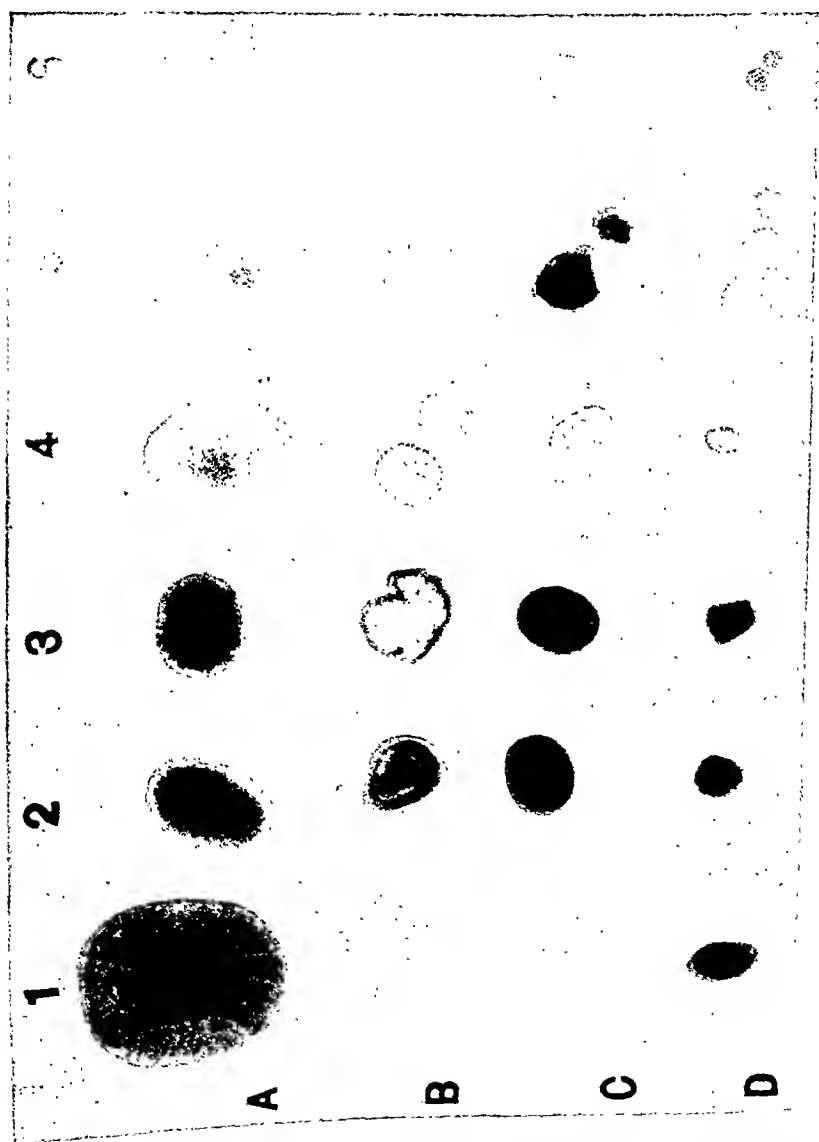


Fig. 2.—X-ray of the stones shown in Fig. 1.

Post-mortem findings of a case of keratomalacia in an infant were reported by Wilson and DuBois in 1923, with keratinization of the epithelium of the renal pelvis.<sup>22, 23</sup> Rats are said to develop keratiniza-

petites of the people for green foods of all kinds. Unripe grapes, green almonds, green apricots, raw cow peas, and lettuce are eaten in large quantities as soon as available. Green leaf vegetables were available only during the winter and spring in the market we studied. The common variety of carrots in Syria is white. Of all the foods which Mendel classes as "excellent sources" of vitamin A, eggs alone were found to be plentiful during the months from April to August.

Further evidence of a lack of vitamin A might be adduced from the occurrence of sporadic cases and epidemics of night blindness,<sup>3</sup> and the prevalence of trachoma and corneal opacities.

The incidence of urinary calculi in the adult population does not fall within the scope of this paper. In children we found no kidney calculi and only one case of ureteral calculus.<sup>2</sup> The symptoms of bladder stone are so dramatic that the diagnosis is easy. The children with bladder stones had been breast fed, but the Syrian mother usually also allows the infant to try to eat any food that is available.

#### CONCLUSIONS

1. Solitary urinary bladder stones are not uncommon in small boys in Syria.
2. The condition is not due to obstruction of the bladder outlet.
3. Neither heredity nor the aridity of the climate nor infections seem to be prime causative factors in this group of cases.
4. Observations are presented which are consistent with the theory that the stones form about keratinized urinary epithelium caused by seasonal vitamin A privation.

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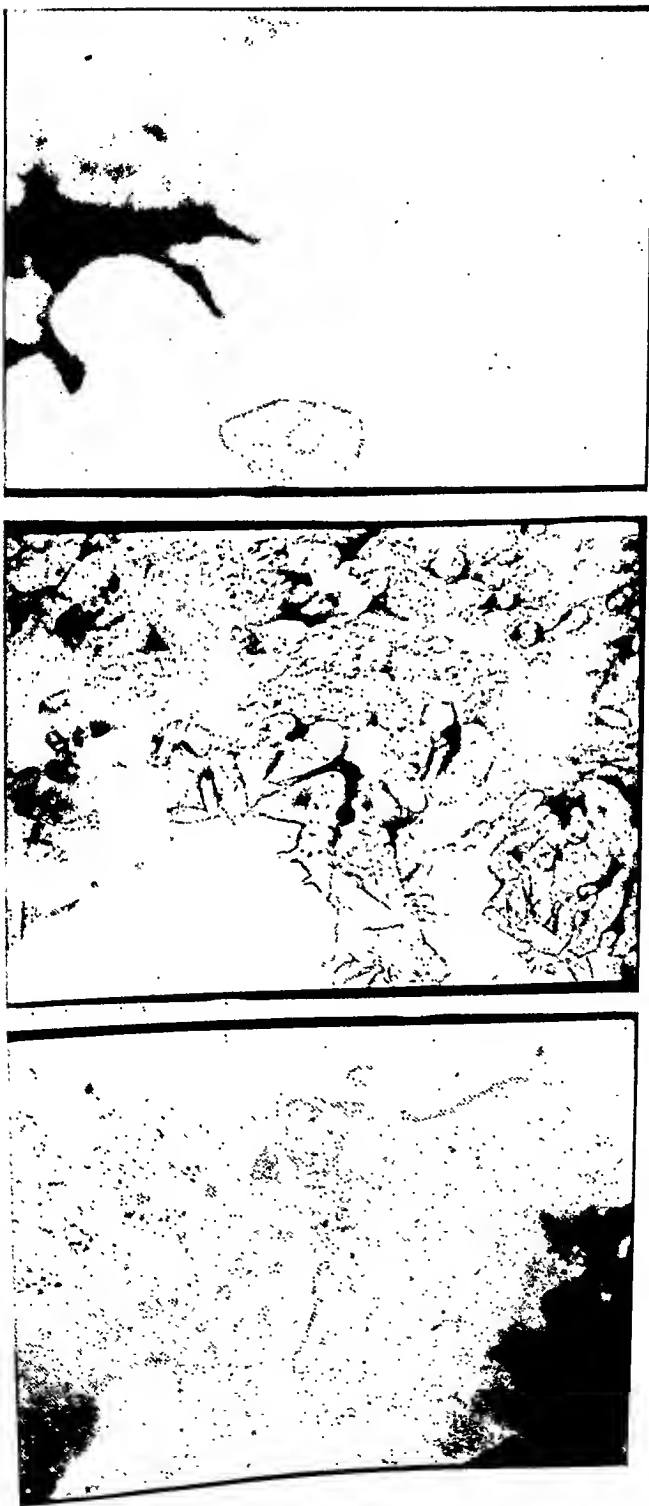


FIG. 3.

FIG. 4.

FIG. 5.

FIGS. 3, 4, and 5.—Photomicrographs of stained smears of substance from the centers of three solitary bladder stones from children. Elements which resemble epithelial cells are seen in all three.

# DISEASE IN THE AMERICAN NEGRO

## I. MELANOMA

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A NUMBER of observers noted the fact that melanoma, in either benign or malignant form, occurs in the negro race with relative rarity.<sup>1-5</sup> Adequate explanation for this surprising fact has not been found. It is intended here to review the facts from previously reported cases and to report ten new cases, so that the rarity and peculiarities of these tumors in the negro may be emphasized.

It is well known that certain types of neoplasms, such as fibromyomas of the uterus, have a greater incidence in the negro. The view seems to persist, however, that malignant tumors are less common in negroes. Adler and Cummings<sup>6</sup> noted the apparent rarity of malignancy in West African natives. Sequeira and Vint,<sup>7</sup> however, do not believe malignancy is rare in African natives, and quote figures from examination of surgical specimens at a native hospital. They found squamous-cell carcinoma of the skin or mucous membranes to be the most frequent type of malignancy and melanoma next. Bishop<sup>1</sup> noted that skin tumors appeared to be less common in the negro, but did not think that there exists any racial immunity to cancer in general. It would seem that in any discussion of racial tendencies to neoplastic growth, particular types of tumors must be compared. Few studies of this nature have been made on the American negro. Extensive investigation of this nature, compared with similar studies from Africa, might reveal additional information about the etiology and nature of cancer.

Matas<sup>8</sup> in 1896, having noted the relative infrequency of melanomas in negroes, suggested that in highly pigmented people the physiologic function of pigment formation was under better biologic control, and so less liable to uncontrolled growth. Morestin<sup>9</sup> reported a melanoma on the foot of a negro. Weiting and Hamdi,<sup>10</sup> in a study of 10,000 deeply pigmented oriental people and negroes in Constantinople, found only 6 melanomas, 2 of which were from the sole of the foot and from the eye. None of the 6 patients were deeply pigmented. Among 7 cases of malignant melanomas reported by Hazen,<sup>11</sup> 1 was in a negro and started on the bottom of the foot. Sutton and Mallia,<sup>12</sup> reviewing this subject in 1923, found reports of only 6 cases of malignant melanoma in the negro, and reported an additional case arising in the toe. Adler and Cummings,<sup>6</sup> in their study of malignancy in West African natives, mentioned 1 case of melanoma which arose from the foot. In 1927 Bauer<sup>13</sup> reviewed the 14 cases which had been reported up to that time and reported 2 cases, 1 arising from a toe and 1 from a thumb.

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Twelve malignant melanomas were observed from white patients during the same period, though the proportion of white patients seen at this institution is only 22 per cent. These figures suggest that malignant melanoma is about four times as frequent (4.2:1) in the white race as in the negro.



Fig. 1.—Case 1. Malignant melanoma of the right hip, as seen on the outer surface, bisected showing the cut surface, and in microscopic section. The abundant melanin pigment is evident.

CASE 1.—A negro woman, aged 26 years, had a small growth on the right hip, present since birth. Two months before admission to the hospital she bruised the tumor and subsequently scratched it. Since that time increase in size had been noted, so that it formed a firm, elevated lobulated dark tumor mass, 4.5 cm. in diameter. The adjacent regional lymph nodes were enlarged, firm, and on section showed dark pigmented areas. The tumor was a papillary type of growth, the neoplastic cells in the subepithelial portion being thin or spindle shaped, but becoming more rounded in deeper portions. In the regional nodes solid dense

Dickson and Jarman<sup>13</sup> reported a case of sublingual melanoma. Bishop<sup>1</sup> reported 9 cases. Butterworth and Klander<sup>14</sup> reported 1 case. Hewer<sup>15</sup> presented figures from the autopsy and surgical pathology laboratories of Johns Hopkins Hospital to indicate the rarity of melanoma in the negro and concluded that melanomas were more than three times as common in white people as in negroes.

Affleck,<sup>5</sup> in a series of 215 benign melanomas, reported only 1 in a negro. Among 317 malignant melanomas, only 2 were in negroes. Individual cases of malignant melanomas in negroes have been reported recently by Herold,<sup>16</sup> Moragues,<sup>17</sup> and Baxter.<sup>3</sup> Paek and Adair<sup>4</sup> in 1939 stated that only 34 cases of melanoma in negroes, excluding African natives, have been reported. Among their series of 477 melanomas, 7 were in negroes. The real rarity of melanomas in American negroes is thus attested by the fact that less than 50 cases have been reported. It is probable, however, that the real incidence is greater than this figure would suggest.

According to a review by Baxter,<sup>3</sup> 224 cases of malignant melanoma have been reported in colored races. The exact number reported from African negro races of the same origin as the American negro and the comparative incidence, is difficult to determine. Several reports indicate that in African natives melanoma may be more common. Des Ligneris<sup>18</sup> noted 17 cases among native patients in Northern Transvaal, all except 1 occurring on the skin of the leg or foot. Sequeira and Vint,<sup>7</sup> as previously noted, found melanomas next in frequency to squamous-cell carcinoma among skin tumors in African natives. Hewer<sup>15</sup> stated that malignant melanomas were frequent among the natives of Anglo-Egyptian Sudan. Baxter<sup>3</sup> concluded that melanotic tumors in the African native often remain locally malignant, less frequently metastasize, and have a slower course than melanoma in the American negro.

Baxter's figures respecting location are interesting. Among 170 cases he collected from the literature, 65.3 per cent occurred on the foot. A definite relationship to trauma appears to be borne out, though it must not be overlooked that the relatively light pigmentation of this region may have some bearing on this frequency of location.

With the exception of Affleck's<sup>5</sup> report, there is a striking absence in the literature of studies on the comparative incidence of benign pigmented nevi in the white and colored races. Such a study should be very instructive, although most of the malignant melanomas reported in the negro have not arisen from previously noted benign growths.

#### REPORT OF CASES

Ten cases of malignant melanoma from negro patients were found among 14,000 surgical specimens at the John Gaston Hospital in Memphis. No cases were observed at autopsy during a five-year period.

pigmented nodules on the foot and left hip. Small nodules could be felt in the left inguinal region.

Microscopic study of the primary tumor of the foot showed marked variation in size, shape, and staining qualities of the tumor cells. The cells were predominantly polygonal in shape. Brownish black intracellular pigment was abundant.



Fig. 3.—Case 8. Sectioned surface of eye, showing the highly pigmented tumor within the chambers of the eye and on the outer surface.



Fig. 4.—Case 9. The left ring finger, showing the large fungating tumor mass involving the end of the finger.

CASE 6.—A negro male, 40 years of age, injured his left foot from a tack in his shoe. A small abscess formed in this area, which discharged purulent material. This remained tender and never completely healed. Nine months later a tender, deeply pigmented area was noted just medial to the point of injury. About the same time a swelling was noted in the left inguinal region. The pigmented region of the foot became slightly elevated and was removed. Pigmented material was prominent in the subepithelial tissue, and irregularly infiltrating downward. The inguinal mass was composed of soft, black tissue. Microscopically, the cells were polyhedral and spindle-shaped, showing considerable variation in morphologic characteristics and numerous mitotic nuclei. Pigment was abundant.

masses were formed by rounded or oval cells with little tendency to be spindle-shaped. Melanin was quite abundant in the tumor and metastases. (Fig. 1.)

CASE 2.—A negro man, aged 55 years, injured his left great toe while working in a lumber yard. The nail was split and he removed it himself, but complete healing never occurred. Four years later the toe was noted to be markedly enlarged, and soon nodules developed on the leg and in the left groin.

Biopsy from the toe showed masses of large pale tumor cells in the subepithelial tissue. Melanin was very abundant. Most of the cells were round or oval, except in focal areas occupied by spindle-shaped cells, with a tendency to pattern formation.



Fig. 2.—Case 4. The primary pigmented ulcerated tumor in the popliteal region and the metastatic tumor mass in the inguinal region.

CASE 3.—A negro female, aged 37 years, developed a painless swelling of the left foot, which grew to form a mass 3 cm. in diameter. Metastasis later developed in the leg. Amputation was performed, but death occurred from intercurrent infection. At the time of amputation the tumor was seen as an ulcer measuring 5.5 cm. situated on the dorsum of the foot. The base of this ulcer was black in color, and the edges were elevated and indurated. Microscopically, most of the cells appeared to be elongated or spindle-shaped forms. Pigment was quite abundant.

CASE 4.—A negro male, aged 73 years, noted a painful nodule on the leg which increased in size and became ulcerated. Nine months later a nodule was present in the left inguinal region which progressed to ulceration, the tumor appearing as a dark grayish black tissue. Microscopically, melanin pigment appeared to be very abundant. Most of the tumor cells had an oval or polyhedral shape, and were arranged in cords or solid sheets. Mitoses were numerous. (Fig. 2.)

CASE 5.—A negro female, aged 25 years, had noticed a small thickening of the skin on the sole of the left foot for eight years. This grew steadily larger and became elevated and tender. A similar nodule appeared on the instep and other

Six months later, following a minor injury to the same finger, a small tumor was noted on the posterior surface of the distal phalanx. This increased in size to form a rounded fungating tumor mass, 6 cm. in diameter. Microscopically, there was but little melanin pigment evident. Mitoses were numerous. The cells varied from oval to spindle shape and were highly anaplastic. (Fig. 4.)

CASE 10.—A negro male, aged 46 years, developed a small black nodular tumor growing out from under the edge of the nail of the left thumb. There was no history of trauma. The thumb was amputated. One year later a small mass was noted in the left axilla. This gradually and painlessly increased in size, forming a very large, lobulated dark brown tumor. The tumor was highly cellular and vascular, with abundant pigment. The cells were polymorphous, being round, polyhedral, and spindle-shaped. (Fig. 5.)

*Comment.*—In this small series of 10 cases the findings emphasized from previously reported cases have been corroborated. In 5 cases the melanoma arose from the foot and in 6 cases there was a definite history of antecedent trauma. An unusually large proportion, 30 per cent, appeared to have a subungual origin. Seventy per cent were derived from regions of the skin which normally contain relatively little pigment. In only 1 case was there a definite history of a previous benign growth at the same site. There seemed to be little significant age or sex difference in this series, though the 4 females varied from 25 to 50 years of age, and the 6 males from 40 to 73 years.

Microscopically, nothing distinctive could be found in this series of malignant melanomas. They appeared quite comparable to the malignant melanomas found in white patients. The tumors varied markedly in the amount of pigment they contained. The morphology of the tumor cells was likewise variable.

Thus, while there seems to be a definite difference in the incidence of malignant melanoma in the white and negro races, no qualitative difference in the tumors has been noted. A definite relationship to traumatic injury is frequent with malignant melanomas in the white race also, though this factor seems unusually prominent in the negro. The incidence of benign pigmented tumors in the negro race does not seem to have been investigated seriously. It is evident, of course, that benign pigmented tumors are apt to be overlooked in heavily pigmented skins unless attention is drawn to them by traumatic injury or malignant change. Consequently the impression obtained from published reports that malignant melanoma in the negro rarely arises from a pre-existing benign growth may be quite misleading. The racial difference in the occurrence of a neuroectodermal tumor, the melanoma, suggests the possibility that investigations of racial incidence of other types of tumors arising from structures of the peripheral or central nervous system may reveal significant facts.

#### SUMMARY

1. Ten cases of malignant melanoma arising in American negroes are reported. These occurred in a series of 14,000 surgical specimens, ap-

CASE 7.—A negro woman, aged 50 years, noticed a small elevation of the skin between the third and fourth toes of the left foot. Four months later, following considerable discomfort from an ill-fitting shoe, the tumor enlarged, became painful and finally ulcerated.

The tumor appeared as a soft, fungating, and ulcerated mass separating the toes. Operative removal of the third and fourth toes, including the tumor mass, was performed. The tumor appeared to have arisen at the junction between dorsal and plantar surfaces.

Microscopically, the tumor cells varied a great deal in shape and size, but were predominantly of spindle form. Mitoses were numerous, and pigment was abundant. The superficial portion of the tumor was infected. Enlarged inguinal lymph nodes showed inflammatory changes but no metastatic tumor cells.



Fig. 5.—Case 10. Showing the very large metastatic tumor mass involving the left axilla.

CASE 8.—A negro male, aged 66 years, became blind in the left eye. Six months later he noted a small round black area, about the size of a pinhead, at the sclerocorneal junction. This gradually increased in size, so that three years later, when medical aid was sought, irregular brownish black masses of soft friable tissue were protruding through the eye.

The eye was enucleated, and the eyeball was found to be practically filled with dark brown tumor tissue, growing beneath the retina and pushing that structure forward. The individual tumor cells were elongated or spindle-shaped and contained abundant melanin pigment. The tumor cells infiltrated the sclera and in some areas had broken through and were proliferating on the external surface of the eye. (Fig. 3.)

CASE 9.—A negro male, aged 59 years, suffered a crushing injury of left ring finger. The fingernail came off, but the wound appeared to heal satisfactorily.

## CROSS-INFECTIONS FROM ANESTHETIC FACE MASKS

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**I**NFECTION from an anesthetic face mask is a known hazard.<sup>1</sup> The possibility of the transmission of influenza by anesthesia apparatus has been suggested.<sup>2</sup> In the presence of active pulmonary tuberculosis with a positive sputum this cross-infection is a real hazard. All too frequently only a cursory washing of anesthetic masks between anesthetics is performed. Autoclaving of apparatus after each anesthesia may be practiced; however, this not only necessitates the use of sterilizing apparatus that often is carrying a capacity load of other operating room supplies, but also demands constant attention by the anesthetist to prevent overheating, with its resultant softening and deterioration of rubber parts. A face mask left in a 10 per cent solution of cresol overnight may cause a skin burn when applied with pressure for a long operation.<sup>3</sup>

We wish to report the results of guinea pig inoculations of saline washings of anesthetic masks removed from patients having active pulmonary tuberculosis. Specimens were taken as follows: (A) after removal of the mask from the face; (B) after washing the mask with water, as is the custom in many institutions; (C) after washing the mask as in (B) and then immersing it for one hour in the following solution:

Formaldehyde (38 per cent solution)	210 c.c.
Aqua	606 c.c.
Alcohol 95 per cent q.s. ad	4,000 c.c.

This solution was made by one of us (G. M. D.) after bacteriologic investigation to determine the lowest percentage of formalin necessary to destroy the tubercle bacilli in less than one hour.

The first specimen (A) was collected from the mask by swabbing it with a sterile swab previously moistened with saline solution. Specimens B and C were saline washings of the entire mask. Specimen A was emulsified in about 2 c.c. of sterile saline solution and injected subcutaneously in guinea pigs. Specimens B and C were individually centrifuged for one hour and the 2 c.c. of the solution in the bottom of the centrifuge flask were removed from each and injected subcutaneously in guinea pigs. These animals were necropsied at the end of eight weeks. Gross evidence of tuberculosis was present at this time; the inguinal lymph nodes were enlarged and caseous and tubercles of the liver, spleen, and other organs were present. In each animal smears were made from this caseous material and acid-fast organisms were demonstrated.

The results obtained from the bacteriologic examination of the anesthetic masks removed from patients with active pulmonary tuberculosis

proximately 78 per cent of which were from negroes. Twelve malignant melanomas were encountered from white patients in the same series of surgical specimens. Thus in this series the relative incidence of malignant melanoma in the white race was more than four times that in the American negro.

2. The frequency with which malignant melanoma in the negro arises in the foot and follows traumatic injury is re-emphasized.

3. No morphologic differences were noted in the malignant melanomas arising in negroes as contrasted with those in the white race.

The author is indebted for the illustrations in this study to Dr. J. L. Scianni, Artist, University of Tennessee Pathological Institute.

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tration and to eliminate the irritating formalin fumes from the apparatus. We have observed no deleterious effect to the patients or the apparatus. This procedure has been employed for seven years in a large series of cases in our institution. The formaldehyde-alcohol solution was preserved for use on several occasions.

#### SUMMARY

Bacteriologic examinations of 39 anesthetic masks removed from patients with active pulmonary tuberculosis revealed contamination with tubercle bacilli in 33.3 per cent of the cases. That these masks must be carefully handled to prevent spread of the disease is obvious.

Over 15 per cent of these masks still contained active tubercle bacilli after the type of washing ordinarily employed and were a potential source for the spread of tuberculosis.

No bacteriologic evidence of tubercle bacilli remained after immersing the masks for one hour in the formaldehyde-alcohol solution described in this communication.

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TABLE I

PATIENT	SPECIMEN			PATIENT	SPECIMEN		
	A	B	C		A	B	C
E. B.	+	-	-	J. B.	+	-	-
A. J.	+	-	-	J. B.	-	-	-
A. J.	-	-	-	J. B.	-	-	-
A. J.	-	-	-	J. H.	-	-	-
R. B.	+	-	-	E. N.	+	-	-
A. N.	-	-	-	R. B.	-	-	-
H. S.	-	-	-	R. B.	-	-	-
W. S.	-	-	-	L. L.	+	-	-
A. M.	+	+	-	(control)			
J. I.	-	-	-	A. M.	+	-	-
J. I.	-	-	-	(control)			
H. S.	-	-	-	A. M.	-	-	-
J. M.	+	+	-	A. M.	-	-	-
E. Bl.	-	-	-	L. L.	+	-	-
E. Br.	Animal died early	+	-	B. J.	-	-	-
				M. B.	+	-	-
				M. B.	-	-	-
				D. M.	-	-	-
D. N.	-	-	-	B. S.	-	-	-
				(control)			
D. N.	-	-	-	B. S.	-	-	-
D. N.	-	-	-	G. (control)	+	+	-
D. N.	+	+	-	R. H.	-	+	-

appear in Table I. In the 39 anesthetic face masks examined 13, or 33.3 per cent, contained tubercle bacilli when removed from the patient's face; 6, or 15.4 per cent, still were contaminated with tubercle bacilli after being washed in water according to the technique all too frequently employed; whereas none contained tubercle bacilli after being washed in water and then soaked for one hour in the formaldehyde-alcohol solution.

#### DISCUSSION

Most, but not all, of the anesthetics administered were for thoracoplasty operations. All of the patients had active pulmonary tuberculosis. Some of the patients had very little sputum at the time of operation, which may account for many of the negative specimens in Column A. It apparently made no difference what stage of thoracoplasty was being performed, as some masks showed contamination on the first stage and others only on later stages. The last patient (R. H.) was known to have a Gaffky 10 sputum. Apparently this sputum was not secured in the swab Specimen A. The results marked "control" indicate the placing of sputum from patients known to have very active pulmonary tuberculosis on face masks and then making the same examinations.

As a routine it has been found practical to remove the anesthetic mask, breathing tubing, breathing bags, head straps, and other removable parts of the anesthetic apparatus from the solution at hourly intervals. After removal, all of these parts should be thoroughly washed with soap and hot water until the odor of formalin cannot be detected. This is necessary in order to avoid a skin burn during the next adminis-

a 0.2 per cent saline suspension of trypan blue is given intravenously into the marginal vein of the ear. Several observations are made on a single rabbit.

Macroscopic examinations are made at frequent intervals. Careful observations over a period of an hour are made following the injection of the trypan blue. The skin becomes blue when the dye localizes. The presence or absence of dye in the areas of hyperemia is recorded and also the size of the area of distribution of the dye.

The original saline suspension of staphylococci is diluted with saline solution 1/10 and 1/100. Intradermal injections of these suspensions are made into some of the rabbits in studying the effects of a variation in the number of bacteria on the quantity of dye that localizes in areas of inflammation. The organisms are heated at 60° C. in a water bath for one hour, placed in the icebox for an hour, after which time they are reheated at the same temperature for a second hour. The heat-killed organisms are usually kept in the icebox overnight before they are injected. Cultures are made on blood agar plates to determine if the bacteria are all killed.

A tuberculin syringe and a 27-gauge needle are used for all intradermal injections.

#### EXPERIMENTAL

*Local Inflammation Produced by Staphylococci in the Skin of the Rabbit.*—Two-tenths cubic centimeter of a saline suspension of washed staphylococci are injected intradermally. Observations are made on the skin at the following intervals (Table I):

TABLE I

TIME	NO. OF RABBITS	MACROSCOPIC OBSERVATIONS
0 min.	11	No change in skin
15 min.	6	No change in skin
30 min.	7	No change in skin
60 min.	9	No change in skin
1½-3 hr.	13	Small amount of hyperemia
4-25 hr.	34	Progressive increase in edema, hyperemia, and frequently focal necrosis

A histologic study on the skin of four rabbits in which the staphylococci are given intradermally at intervals varying from fifteen minutes to twenty-four hours before the animals are killed shows a progressive increase locally in the number of leucocytes. Definite abscesses are present two hours after the bacteria are injected. Some thrombosed vessels are present; however, they are infrequent.

The time in which the leucocytes first appear in the tissues where the killed bacteria are injected is approximately the same as when they appear in the areas injected with the live organisms.

*Localization of Trypan Blue in Areas of Inflammation Produced by Staphylococci.*—The preceding experiments show that the macroscopic

# OBSERVATIONS ON CAPILLARY PERMEABILITY IN AREAS OF INFLAMMATION PRODUCED BY STAPHYLOCOCCI\*

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IT HAS been shown recently that trypan blue following an intravenous injection in the rabbit localizes and concentrates in areas of inflammation produced by the local application of xylol only when the dye is given within a period of three hours following the application of the irritant. The skin remains hyperemic and edematous, however, for several days following the application of xylol.<sup>1, 2</sup>

Menkin in studying inflammation injected 0.1 c.c. of a saline suspension of *Staphylococcus aureus* into the dermis of the abdomen of rabbits and a few hours later gave the animals an intravenous injection of trypan blue. He observed that "within a relatively short time the tissues in the site of inflammation appeared markedly stained. In many cases these areas showed a pale reddish central zone surrounded by an intensely dark blue band measuring about 0.5 cm. in width. The localization of intravenously injected trypan blue in inflamed areas of the dermis was evident in thirty-two out of thirty-six experiments. The central zone which has a red congested appearance and which is often seen in these intracutaneous areas of inflammation is perhaps due to thrombosis of small vessels. Histological sections of such areas reveal some thrombosed vessels with acute inflammatory changes in the surrounding tissue."<sup>3</sup>

It is important to compare the localization and concentration of trypan blue in areas of inflammation produced by staphylococci with that which occurs following the application of xylol. Especial attention is given in this study to the interval between the intradermal injection of organisms and the intravenous injection of the trypan blue.

## MATERIAL AND METHODS

Normal rabbits are used in this study. They are carefully shaved twenty-four hours or longer before the experiment is begun.

The staphylococci are grown on extract agar at 37.5° C. for twenty-four hours. The bacteria are washed with saline solution from the agar surface and then washed three times in large volumes of physiologic salt solution. The organisms are suspended in saline solution. The concentration is sufficient to make a cloudy suspension. Two-tenths cubic centimeter of this bacterial suspension is injected intradermally at intervals varying from twenty-five hours to immediately before 10 c.c. of

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*Observations on the Localization of Trypan Blue in Areas of Inflammation Produced by Killed Staphylococci.*—The preceding experimental observations show that edema and hyperemia apparently are not the factors that determine the localization of trypan blue in areas of inflammation. A saline suspension of killed staphylococci when injected intradermally in the rabbit produces hyperemia and edema and polymorphonuclear leucocytes infiltrate the local area of the corium. To study the localization of trypan blue in areas of inflammation produced by killed staphylococci four rabbits are given intradermally killed organisms suspended in saline solution at varying intervals before 10 c.c. of trypan blue is injected intravenously. Table III illustrates the results observed in these rabbits. This chart also shows the variation in

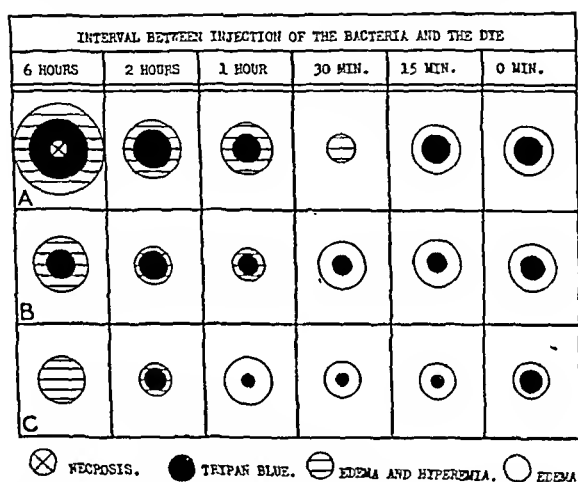


Fig. 1.—Localization of trypan blue in areas of inflammation produced by staphylococci. A, Suspension of staphylococci; B, a diluted 1/10; C, a diluted 1/100. Observations on necrosis, hyperemia, and edema made immediately before 10 c.c. of 0.2 per cent trypan blue was given intravenously. Location of dye recorded thirty minutes following injection.

TABLE III

LOCALIZATION OF TRYPAN BLUE FOLLOWING AN INTRAVENOUS INJECTION IN AREAS OF SKIN PREVIOUSLY INJECTED INTRADERMALLY WITH HEAT-KILLED STAPHYLOCOCCI\*

SUSPENSION† OF STAPHYLOCOCCI	INTERVAL BETWEEN INJECTION OF BACTERIA AND DYE				
	3 HR.	2 HR.	1 HR.	30 MIN.	0 MIN.
Undiluted	Hyperemia and edema	Hyperemia and edema	Hyperemia and edema	No reaction	No reaction
	No dye	No dye	Dye‡	Dye	Dye
1/10	Hyperemia and edema	Hyperemia and edema	No reaction	No reaction	No reaction
	No dye	No dye	Dye	Dye	Dye
1/100	No reaction	No reaction	No reaction	No reaction	No reaction
	No dye	No dye	Dye	Dye	Dye

\*These observations were recorded thirty minutes following the intravenous injection of 10 c.c. of 0.2 per cent suspension of trypan blue.

†Milky suspension of heat-killed staphylococci in saline solution.

‡This dye was only around the point of entry of the needle and approximately an equal amount was present where each of the three dilutions of the staphylococci was injected.

evidence of inflammation produced by the staphylococci used in this study occurs only after one hour. Polymorphonuclear leucocytes begin to infiltrate the tissues, however, after only a few minutes.

The rabbits used in the preceding experiment were injected intravenously with trypan blue. The following data (Table II) are the macroscopic observations on the localization of trypan blue in the areas of skin previously injected with the bacteria. These observations are made within fifteen minutes following the injection of the dye.

TABLE II

TIME	NO. OF RABBITS	MACROSCOPIC INFLAMMATION	LOCALIZATION OF TRYPAN BLUE
0 min.	11	None	Small amount of dye at point of entry of needle
15 min.	6	None	Small amount of dye
30 min.	7	None	} Largest amount of dye localized during this period
45-60 min.	9	None	
1¼-1½ hr.	4	Hyperemia and edema	
2-3 hr.	10	Hyperemia and edema	A smaller amount of dye than observed between 30 min. and 1½ hr.
4-5 hr.	4	Skin shows hyperemia, edema, and necrosis	} Only a narrow zone of dye is present around the periphery of the necrotic areas
6-8 hr.	4	Skin shows hyperemia, edema, and necrosis	
16-20 hr.	13	Skin shows hyperemia, edema, and necrosis	
21-25 hr.	13	Skin shows hyperemia, edema, and necrosis	

It is evident from the above data that trypan blue localizes in areas of skin where staphylococci have been previously injected when there is no macroscopic evidences of inflammation. Furthermore the greatest quantity of dye localizes in areas of inflammation when it is given intravenously within a period of three hours following the intradermal injection of the bacteria. When there is hyperemia, edema, and necrosis only a narrow zone of trypan blue localizes at the periphery of the necrotic area.

Four rabbits are given 0.2 c.c. of the following dilutions of staphylococci intradermally in studying the effect that a variation in number of staphylococci might have on the localization of trypan blue in areas of inflammation; the original suspension, 1/10 and 1/100 dilutions of the original suspension. The bacteria are injected intradermally at varying intervals preceding the intravenous injection of 10 c.c. of trypan blue. Fig. 1 shows the location of trypan blue in the skin in one of these rabbits after thirty minutes. It appears that the quantity of dye that localizes in areas of inflammation is only partly influenced by the number of bacteria injected. After ten minutes there is no dye in any of the areas where a 1/100 dilution of this suspension of staphylococci is given to two of these four rabbits. There is a diminution in the size of the areas of inflammation and the amount of dye where the 1/100 dilution is injected as compared with the undiluted suspension.

*Observations on the Localization of Trypan Blue in Areas of Inflammation Produced by Killed Staphylococci.*—The preceding experimental observations show that edema and hyperemia apparently are not the factors that determine the localization of trypan blue in areas of inflammation. A saline suspension of killed staphylococci when injected intradermally in the rabbit produces hyperemia and edema and polymorphonuclear leucocytes infiltrate the local area of the corium. To study the localization of trypan blue in areas of inflammation produced by killed staphylococci four rabbits are given intradermally killed organisms suspended in saline solution at varying intervals before 10 c.c. of trypan blue is injected intravenously. Table III illustrates the results observed in these rabbits. This chart also shows the variation in

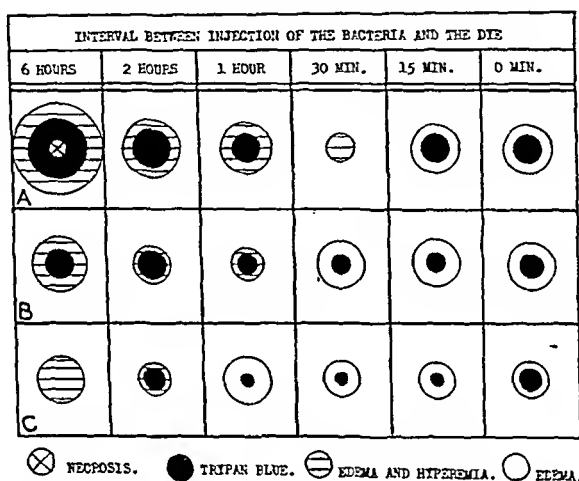


Fig. 1.—Localization of trypan blue in areas of inflammation produced by staphylococci. *A*, Suspension of staphylococci; *B*, a diluted 1/10; *C*, a diluted 1/100. Observations on necrosis, hyperemia, and edema made immediately before 10 c.c. of 0.2 per cent trypan blue was given intravenously. Location of dye recorded thirty minutes following injection.

TABLE III

LOCALIZATION OF TRYPAN BLUE FOLLOWING AN INTRAVENOUS INJECTION IN AREAS OF SKIN PREVIOUSLY INJECTED INTRADERMALLY WITH HEAT-KILLED STAPHYLOCOCCI<sup>2</sup>

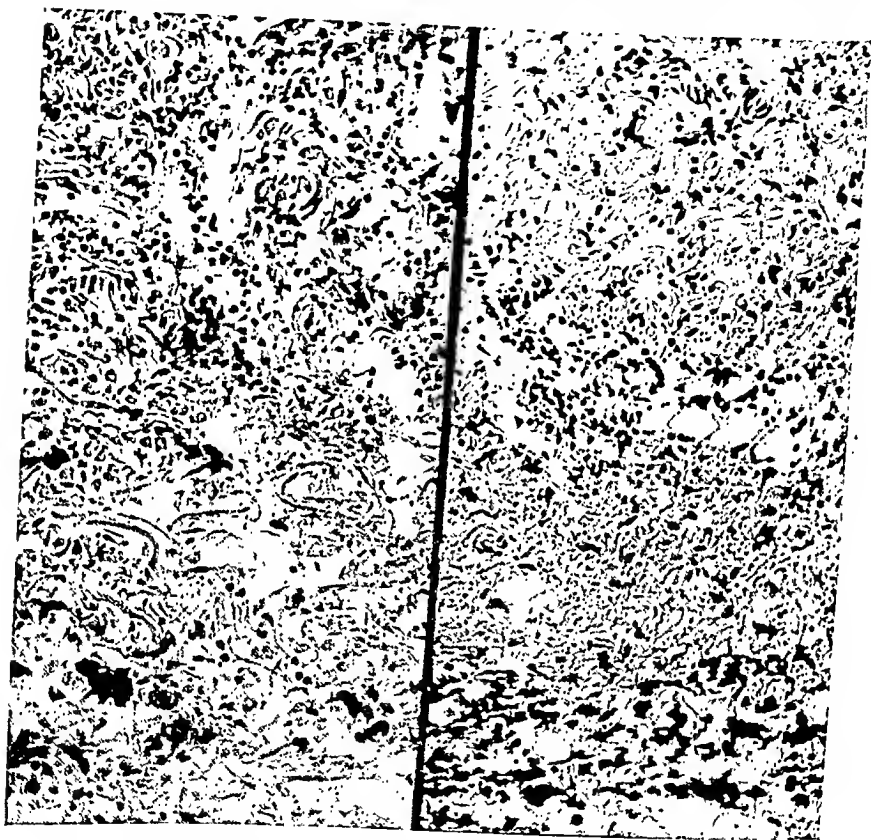
SUSPENSION† OF STAPHYLOCOCCI	INTERVAL BETWEEN INJECTION OF BACTERIA AND DYE				
	3 HR.	2 HR.	1 HR.	30 MIN.	0 MIN.
Undiluted	Hyperemia and edema No dye	Hyperemia and edema No dye	Hyperemia and edema Dye‡	No reaction Dye	No reaction Dye
1/10	Hyperemia and edema No dye	Hyperemia and edema No dye	No reaction Dye	No reaction Dye	No reaction Dye
1/100	No reaction No dye	No reaction No dye	No reaction Dye	No reaction Dye	No reaction Dye

\*These observations were recorded thirty minutes following the intravenous injection of 10 c.c. of 0.2 per cent suspension of trypan blue.

†Milky suspension of heat-killed staphylococci in saline solution.

‡This dye was only around the point of entry of the needle and approximately an equal amount was present where each of the three dilutions of the staphylococci was injected.

the degree of reaction produced by the different dilutions of the killed organisms. Edema, hyperemia, and polymorphonuclear leucocytes may be present, but trypan blue when given intravenously fails to localize in some of the areas. There is a very small amount of trypan blue after five minutes, located about the point of entry of the needle with each of the three dilutions of bacteria injected immediately before the dye is given. Essentially the same amount of dye is present in the two



A.

B.

Fig. 2.—A, 0.2 c.c. of a saline suspension of staphylococcus was injected intradermally one hour and fifteen minutes before the section was removed. Many polymorphonuclear leucocytes are present. Groups of staphylococci are present. A large amount of dye localized in this area immediately following an intravenous injection of 10 c.c. of trypan blue. B, 0.2 c.c. of a saline suspension of heat-killed staphylococci was injected intradermally and the section was removed after one hour and fifteen minutes. Leucocytes and groups of staphylococci are present. Very little dye localized here following an intravenous injection of trypan blue.

areas of skin injected with the undiluted suspension of bacteria thirty minutes and one hour before the dye is given. Thirty minutes following the injection of trypan blue essentially the same amount of dye is present in those areas injected with each of the three dilutions of bacteria immediately, thirty minutes, and one hour before the trypan blue is injected.

Several rabbits are injected with both live and heat-killed suspensions of staphylococci. Trypan blue localizes in certain of the areas injected with the live organisms and does not localize in the corresponding areas injected with the killed bacteria. Fig. 2 shows the local leucocytic reaction where live and heat-killed organisms are injected one hour and fifteen minutes previous to the removal of these sections. Trypan blue when given intravenously stains the areas where the live bacteria are, while essentially no dye localizes in the area where the heat-killed bacteria are located.

#### DISCUSSION

The observations made in this experiment show that trypan blue following an intravenous injection may localize in areas of skin previously injected with staphylococci when there is no evidence of macroscopic inflammation. The localization of trypan blue in areas of skin injected intradermally with staphylococci apparently cannot be correlated with either edema, hyperemia, or the presence of leucocytes. Similar observations were made on the localization of trypan blue in areas of inflammation produced by the local application of xylol. In the experiment with xylol the greatest quantity of dye localized in the last area where the irritant was applied immediately before the dye was given.<sup>2</sup>

The present experiments support the observations and opinion previously expressed on the relation of capillary permeability as shown by the localization of trypan blue to local leucocytosis.<sup>2</sup> It would appear that the rabbit's skin becomes blue following an intravenous injection of trypan blue as a result of a change in the permeability in the capillaries and extravascular cells. This change in the permeability may occur simultaneously with edema and hyperemia; however, it may be absent in areas of edema and hyperemia as shown by the failure of such areas to stain blue following the intravenous injection of trypan blue.

It is suggested that the staphylococcus may elaborate a substance in vivo which injures tissue cells. If the injury is mild, the cell will take up the colloidal particles of trypan blue. If the injury is severe and the cell is destroyed, it cannot take up the dye and thus the area of necrosis will not become blue. This opinion is based upon the diffuse localization of trypan blue in those areas where staphylococci are injected within a period of three hours before the dye is injected. At this time apparently the permeability of the greatest number of cells is changed, permitting the localization of the dye either in or on the cells. Edema and hyperemia may be present in other areas of the same rabbit; however, there occurs a diminution in the quantity of trypan blue that will localize when the organisms are injected several hours previously.

Thrombosed capillaries do occur in areas of inflammation as pointed out by Menkin<sup>3</sup>; however, an insufficient number of such vessels have been found in these experiments apparently to account for the failure of

trypan blue to reach areas of inflammation where the bacteria are injected six to twenty-four hours previously.

In any study on the localization of a dye in areas of inflammation it appears important to make frequent observations immediately following the injection of the dye in order to separate localization and concentration from retention of colloidal dyes in areas of inflammation. It has been shown that trypan blue is always retained for a longer time in those tissues that show inflammatory changes than in the normal skin.<sup>2</sup> It must also be remembered that the interval in which trypan blue may localize in areas of skin previously injected with staphylococci will be influenced by the virulence of the bacteria, the number of organisms, and the susceptibility of the animal.

#### SUMMARY

Trypan blue when given intravenously to rabbits localizes and concentrates in areas of skin previously injected with a saline suspension of staphylococci in the greatest quantity where the bacteria are injected within a period of three hours previous to the injection of the dye.

There is no relation between edema and hyperemia and the localization and concentration of trypan blue in areas of inflammation produced by staphylococci.

Essentially no dye localizes in areas of the rabbit's skin previously injected with killed staphylococci, although corresponding areas injected with live organisms in the same rabbit will become blue following an intravenous injection of trypan blue.

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# Editorial

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## The Sphincter of Oddi

RECENT anatomical and physiological studies have revealed anew the complexity of that sheath of intrinsic muscle fibers which encloses the common bile duct in its short course through the wall of the duodenum. Improved maceration techniques<sup>1</sup> indicate that, in addition to newly described "reinforcing fibers" which strengthen the corners of the window through which the duct enters the duodenum and "connecting fibers" which tie the duct to the margins of the window and help erect the papilla, there are three sphincter bands which are present in varying degree in different individuals. Of these, the *sphincter choledochus*, a well-developed sheath of muscle fibers encircling the bile duct from its entrance into the duodenum to its junction with the pancreatic duct, is the one muscle (in the varying patterns of termination of these ducts) that is always so placed as to obstruct the flow of bile and to cause it to back up into the gall bladder during intervals between meals.

The second ring, the *sphincter pancreaticus*, encloses the end of the pancreatic duct just before it joins the bile duct in about one-third of all individuals. The part it plays in regulating the flow of pancreatic juice is not yet apparent, but it is of interest to note that in the chimpanzee the duodenal portion of the accessory pancreatic duct is always enclosed by a strong sphincter.<sup>2</sup>

The third ring, the *sphincter ampullae*, is well developed in only one-sixth of all individuals. Curiously enough, this is approximately the percentage of patients in whom reflux of contrast media into the pancreatic duct has been demonstrated by cholangiography,<sup>3, 4</sup> the implication being that in this percentage of the population spastic contraction of the muscle around the ampulla of Vater creates a common passage through which the contents of one duct may pass into the other. More recently the reflux of pancreatic juice into the biliary tract has been demonstrated in man<sup>5</sup> and has been proved to be an agency for the production of pigment stones in an experimental animal.<sup>6</sup>

Physiologically, there now exist experiments upon cholecystectomized and choledochostomized patients which have tested simultaneously the pressure and rate of flow in the common bile duct and the pressure in the duodenum following sudden distention of the common duct. These have demonstrated not only that the human sphincter of Oddi can act independently of the duodenal musculature, but that the intense pain induced by suddenly distending the common bile duct can be correlated only with spasm of the sphincter.<sup>7, 8</sup>

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# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## RECENT ADVANCES IN THE STUDY AND MANAGEMENT OF TRAUMATIC SHOCK

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(Continued from the February issue.)

### V. SHOCK IN VARIOUS CONDITIONS

The following summary shows the similarity between the shock that occurs in many medical and surgical conditions. The list of conditions is not complete and it is to be remembered that similarity and likeness are not to be confused. In all, or almost all, of these conditions shock is due to more than one factor, and it is only by analyzing the proper proportions in each case that a complete understanding can be gained.

*Traumatic Shock.*—Shock due to trauma is one of the most common forms of shock, especially in this day of the automobile and the Axis. The importance of local blood and fluid loss in experimental traumatic shock has already been pointed out. Wilson and Roome (1933) presented a dramatic clinical case confirming this experimental work, and four years later Harkins and Roome (1937) presented a study of ten cases demonstrating the same point. These latter authors found that concealed hemorrhage and extravasation of plasma into the tissues are usually greater when measured quantitatively than casual inspection of the resultant swelling would lead one to believe. Mahoney (1938) performed additional trauma to the extremity experiments with resultant decreases in the blood pressure, blood volume (and especially in the erythron), total circulating protein, and in hemoconcentration.

*Hemorrhagic Shock. Shock Due to Whole Blood Loss.*—This is an important factor in many types and examples of shock. The article of Lehman and Amole (1938) emphasizes the function of the spleen in the retardation of shock from hemorrhage. Recently recovered splenectomized dogs did not stand repeated withdrawals of blood as well as normal dogs.

*Intra-Abdominal Apoplexy.*—This type of shock due to spontaneous rupture of an abdominal visceral artery is discussed by Thompson and Dunphy (1935) and by Crile and Newell (1940). Bartlett and Bartlett (1933) also reported on shock due to intraperitoneal hemorrhage.

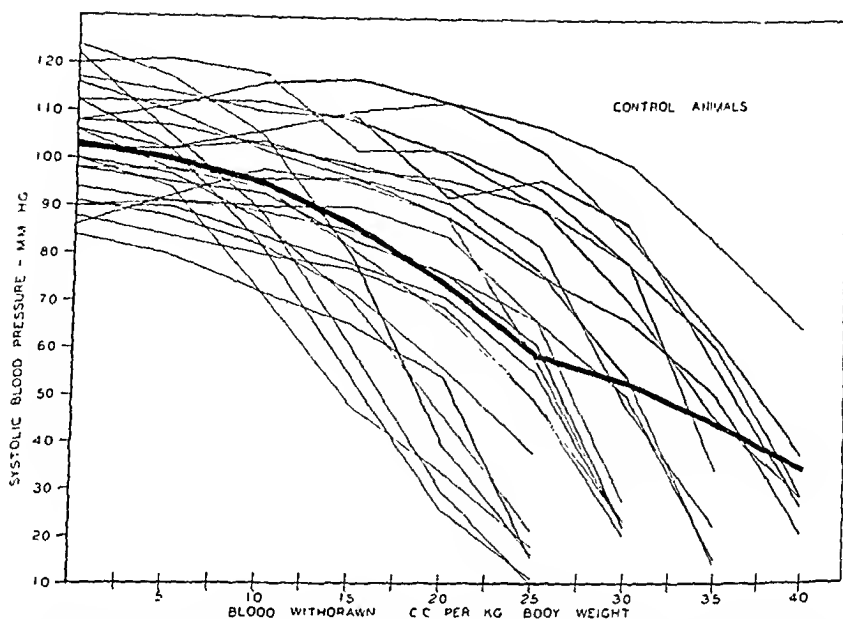


Fig. 4.—Blood pressure fall following hemorrhage in control dogs. The fine lines represent individual and the heavy line the average arterial blood pressure curves during withdrawal of 5 c.c. of blood per kilogram of body weight at five-minute intervals. (From Lehman, E. P., and Amole, C. V.: *SURGERY* 4: 47, 1938.)

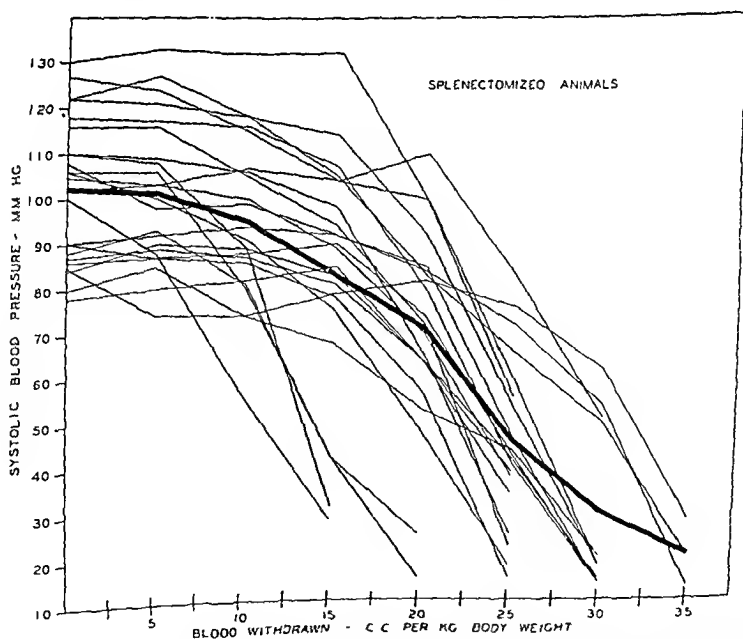


Fig. 5.—Blood pressure fall following hemorrhage in splenectomized dogs. Individual and average arterial blood pressure tracings during withdrawal of 5 c.c. of blood per kilogram of body weight at five-minute intervals. (From Lehman, E. P., and Amole, C. V.: *SURGERY* 4: 47, 1938.)

*Shock During Operations. Operative Shock.*—The important observation of Livingstone, McFetridge, and Brummer (1933) that during anesthesia "blood pressure changes, rather than an increase in pulse rate frequently present the earliest evidence of circulatory failure," should be remembered by every anesthetist. It should also be noted that, while the pulse rate is often misleading, the blood pressure often is as well. Gatch and Little (1924) determined the blood loss during surgical operations by testing the sheets, sponges, etc., and found it greater than was anticipated (mastectomy, 710 c.c.; nephrectomy, 816 c.c.; laminectomy, 672 c.c., etc.). They advised large (3 liters if indicated) transfusions to counteract this direct blood loss.

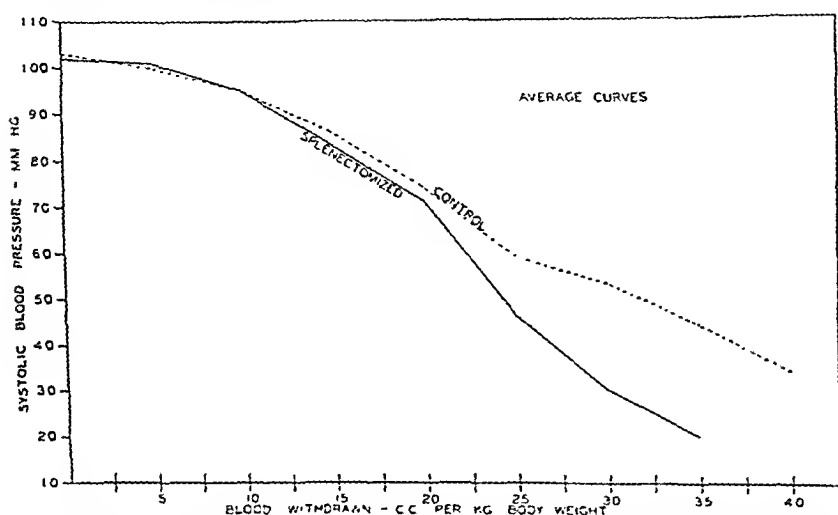


Fig. 6.—Comparison of blood pressure curves in control and splenectomized dogs following hemorrhage. (From Lehman, E. P., and Amole, C. V.: *SURGERY* 4: 48, 1938.)

TABLE VIII  
CONDITIONS IN WHICH OLIGEMIC SHOCK MAY OCCUR

1. Hemorrhage—to outside, into tissues, into body cavities
2. Mechanical trauma—operative, accidental, trauma to intestines
3. Thermal trauma—burns, freezing, peritoneal cooling
4. Asphyxial trauma—mesenteric vascular occlusion, intestinal strangulation, tourniquet, heat stroke
5. Actinic trauma—radiation burns, sunburn
6. Chemical trauma—bile peritonitis, perforated peptic ulcer, acute pancreatitis (?), war gas poisoning
7. Trauma due to specific or nonspecific poisons—mercuric chloride, arsenicals, gold chloride, snake venom
8. Special capillary poisons—tissue autolysis, histamine, anaphylaxis, peptone
9. Medical conditions—diabetic coma, eclampsia
10. Infections—cholera, pneumonia (especially influenzal and streptococcal), gas gangrene, diphtheria, peritonitis
11. Hyperventilation
12. Spinal anesthesia

Coller and Maddock (1932) confirmed Gatch's observations and concluded: "In general, the operator is surprised to find the blood loss as high as calculated, since he does not think of the gauze sponge as absorbing much blood. . . . It is probable that most surgeons underestimate the amount of blood lost, especially in operations . . . in which wide areas of the body are uncovered with many small points of hemorrhage, control of which is attempted by gauze packing." One patient upon whom radical mastectomy was performed under nitrous oxide-oxygen anesthesia lost 1,272 c.c. of blood.

*Relation of General Anesthesia and Shock.*—Stewart and Rourke (1938) made studies similar to those of Mann and his co-workers, only on the effects of operation and ether anesthesia in man. They reported a lowering of plasma volume, often greater than the measured blood loss at operation would explain. Adolph, Gerbasi, and Lepore (1934) believed that amytal caused the spleen to discharge its red cells. Adolph and Gerbasi (1933) found that intraperitoneal sodium amytal administration in dogs led to a blood dilution. The results of Elman, Weiner, and Cole (1935) are not entirely compatible with this, for they found that the usual dilution of blood occurring in dogs after a single large hemorrhage under local anesthesia is absent when a similar hemorrhage is performed after the induction of intravenous sodium amytal anesthesia. There may even be concentration of the blood in the latter case. Seeley, Essex, and Mann (1936) found that the exudation from experimentally traumatized intestines is much less under amytal than under ether anesthesia. Amytal caused an immediate blood dilution and definitely delayed the eventual hemoconcentration and onset of shock. The series of animals experimented upon under ether, on the other hand, developed immediate and rapid hemoconcentration. Essex, Seeley, Higgins, and Mann (1936) found that ether anesthesia in the dog causes a marked increase in the erythrocyte count and the value for the hemoglobin and the hematocrit value, while sodium amytal causes the spleen to dilate markedly, which removes a considerable percentage of erythrocytes from the circulation. These results agreed with those of Searles and Essex (1936), who showed that ether anesthesia produces a hemoconcentration while amytal anesthesia results in a hemodilution.

Murphy (1940), in discussing the question of anesthesia in shock, pointed out the possible hazards of morphine. Kabat (1940) emphasized that general anesthesia (ether) increases the susceptibility of cats to shock. This may be due to the attendant decrease in muscle tone with poor venous return, to the decreased ability to adjust to changes in blood pH, and possibly to the exaggeration of depressor reflex activity. Kabat believes that spinal anesthesia may exert a beneficial effect, but puts forward no evidence to support this conclusion in his article.

A recent discussion in the *Lancet* (1940-1941) on the question of whether local or general anesthesia is best in shock is of interest. Clarke and Kessel (1940) advised local anesthesia, whereupon an editorial (Dec. 21), Hewer (1940), and Macintosh attacked this view, while Dodd (1941) and Henry (1941) supported it. The results of Pickering, Steinmeyer, and Luckhardt (1938) on the hemodynamic effects of procaine are apropos to this discussion.

*Spinal Anesthesia.*—The comprehensive monograph by Schubert (1936) on the circulation in spinal anesthesia indicated from both experimental and clinical observations that the low blood pressure accompanying spinal anesthesia is a type of secondary shock. This author showed by detailed studies that there was a moderate decrease in the oxygen consumption, a slight decrease in the oxygen content of arterial blood, and a considerable decrease in the oxygen content of the venous blood and in the cardiac output per minute. However, the absence of blood concentration and of a decrease in the blood volume differentiated spinal anesthesia shock from other types of true secondary shock. Goldfarb, Provisor, and Koster (1939) have also studied circulation during spinal anesthesia.

*Shock Due to Plasma Loss.*—As discussed elsewhere, the loss of plasma is no less dangerous than that of whole blood, even though the red color that is associated with danger is absent from the lost fluid. "White" hemorrhage may be even more menacing than red. Harkins and Harmon (1937) reviewed the literature and collected data on the occurrence of plasma loss in ten conditions. They concluded that:

"(1) Plasma-like fluid is lost from the blood stream in a variety of conditions. These include burns, freezing, bile peritonitis, tissue autolysis in vivo, acute pancreatitis, pneumonia and pulmonary edema, intestinal manipulation, portal and mesenteric obstruction, externally strangulated colostomy loops, and release of a constrictor of an extremity.

"(2) The types of trauma which produce these conditions can be roughly divided into (1) thermal trauma, (2) chemical and bacterial trauma, (3) mild continued mechanical trauma, and (4) capillary injury due to inadequate circulation.

"(3) The amount of plasma-like fluid lost in these conditions approaches that which, when removed experimentally in plasmapheresis experiments, will produce death. Even in cases where the amount of fluid lost is not sufficient to cause death, it is often of sufficient importance to be recognized."

The data upon which these conclusions were based are summarized in Tables IX to XII. Many of the following conditions in which shock occurs are accompanied by an extensive plasma loss.

TABLE IX

A COMPARISON OF THE CONCENTRATION OF CERTAIN SUBSTANCES IN BLOOD PLASMA  
AND IN THE FLUID LOST FROM THE BLOOD STREAM  
IN VARIOUS CONDITIONS\*

FLUID	SUGAR	NaCl MG. PER 100 C.C.	NONPROTEIN NITROGEN	PROTEIN GM. PER 100 C.C.
1. Burns	134	686	66	7.6
2. Freezing	67	697	50	3.6
3. Bile peritonitis	60	516	32	4.3
4. Tissue autolysis in vivo	83	565	71	7.6
5. Acute pancreatitis	No data	No data	No data	No data
6. Pneumonia and pulmonary edema	No data	631	No data	No data
7. Intestinal manipulation	221	616	61	6.2
8. Mesenteric obstruction	215	577	36	3.0
9. Externally strangulated colostomy loops	137	689	21	4.5
10. Release of a constrictor of an extremity	No data	619	47	4.4
Average	131	622	48	5.2

\*Control values for blood plasma were: sugar, 104; NaCl, 676; nonprotein nitrogen, 54 mg. per 100 c.c.; protein, 4.2 Gm. per 100 c.c.

TABLE X

BLEEDING VOLUME IN VARIOUS CONDITIONS IN WHICH PLASMA HEMORRHAGE OCCURS\*

CONDITION	BLEEDING VOLUME PER CENT BODY WEIGHT
1. Burns	1.6
2. Freezing	2.0
3. Bile peritonitis	1.8
4. Tissue autolysis in vivo	2.2
5. Acute pancreatitis	No data
6. Pneumonia and pulmonary edema	No data
7. Intestinal manipulation	1.4
8. Mesenteric obstruction	No data
9. Externally strangulated colostomy loops	No data
10. Release of a constrictor of an extremity	No data
Average	1.8

\*Control values for the bleeding volume of animals under barbital have been reported: 5.2, 4.5, and 4.17 per cent of body weight. In primary types of shock the bleeding volume is usually above 3 per cent (e.g., following histamine injections, 3.6 per cent), and in secondary types of shock is below 3 per cent (e.g., following trauma to an extremity, 1.7 per cent).

*Burns.*—The literature on this subject has recently been reviewed by Harkins (1938), so only a brief mention of a few reports will be made at this time. Harkins, Wilson, and Stewart (1935) found no evidence of toxic action in protein-free extracts of burned skin. Harkins (1934-1938) in a series of eight papers studied burns especially from the standpoint of fluid loss and shock. This work was essentially an extension of that of Blalock (1931) and its chief contribution was the obtaining of a time curve of the edema at the site of the burn by means of a tipping apparatus connected with a kymographie tracing. The one side of an anesthetized animal which was burned gradually

TABLE XI

BLOOD CONCENTRATION IN VARIOUS CONDITIONS IN WHICH PLASMA HEMORRHAGE OCCURS

CONDITION	HEMOGLOBIN:	HEMATOCRIT:
	INCREASE AS PER CENT INCREASE OVER CONTROL READING	INCREASE AS PER CENT INCREASE OVER CONTROL READING
1. Burns	27	28
2. Freezing	40	40
3. Bile peritonitis	48	43
4. Tissue autolysis in vivo	37	42
5. Acute pancreatitis	No data	No data
6. Pneumonia and pulmonary edema	66	No data
7. Intestinal manipulation	48	No data
8. Mesenteric obstruction	57	No data
9. Externally strangulated colostomy loops	No change	No change
10. Release of a constrictor of an extremity	No data	No data
Average	46	38

TABLE XII

TOTAL PLASMALIKE FLUID RECOVERED IN VARIOUS FATAL CONDITIONS EXPRESSED AS PERCENTAGE OF BODY WEIGHT\*

CONDITION	LOSS OF PLASMALIKE FLUID IN PER CENT BODY WEIGHT
1. Burns	3.2, 2.2
2. Freezing	2.6
3. Bile peritonitis	2.5
4. Liver autolysis peritonitis	2.6
5. Acute pancreatitis	No data
6. Pneumonia and pulmonary edema	No data
7. Intestinal manipulation	No data
8. Mesenteric obstruction	5.2
9. Externally strangulated colostomy loops	No data
10. Release of a constrictor of an extremity	3.5
Average	3.1

\*Control values in death following plasmapheresis have been reported as 2.6 per cent body weight (Johnson and Blalock, 1931), 4 per cent (Harkins and Harmon, 1937) and 4.4 per cent (Roome, Keith, and Phemister, 1933).

became heavier than the unburned side and the curve of this increase in weight gave a quantitative record of the increase in local edema. In previous experiments Blalock burned one side of thoroughly anesthetized animals and found at death that the weight of the two sides after bisection indicated an excess in weight of the burned side averaging 3.34 per cent of the body weight. More recent observations on burns include the following: Wilson, Rowley, and Gray (1936) and Wilson and Stewart (1940) found adrenal cortical extract of help in the treatment of burns. Trusler and associates (1939) used transfusions in burn treatment. Gunther (1939) stated that stasis in small vessels is an important factor in shock due to burns. Elkinton (1939) has added new evidence to the theory that fluid loss is of importance in burns. Greenwald (1940) discussed the overactivity of the adrenals

in the early stage. The paper of Keeley, Gibson, and Pijoan (1939), demonstrating the decreased blood and plasma volume in burns, is of importance. It not only confirms the results of previous workers but makes the conclusions more accurate, the new dye (Evans blue) method being used in these determinations. It is to be remembered that late deaths following burns are not due to shock in many instances any more than are late deaths after operation. Blalock (1934) realized that what causes death at an early period in a disease is not necessarily the fatal factor all through it. With regard to burns, still retaining his ideas as to the importance of fluid loss in the early hours, he stated: "I believe that deaths which occur from three to ten days following severe burns are due in large part to the absorption of protein decomposition products."

*Freezing.*—Harkins and his associates (1934-1937) found that the changes accompanying experimental local freezing are quite comparable to those resulting from its thermal relative, burning. Thus, hemoconcentration, lowered bleeding volume, decreased blood pressure, and decreased blood flow occurred. However, these observations are of little practical interest since local freezing of this extent rarely occurs, the patient usually succumbing to the general effects of the cold before shock can intervene.

*Roentgen Irradiation Shock.*—Moon, Kornblum, and Morgan (1940, 1941) reported a shocklike condition accompanied by hemoconcentration following experimental roentgen radiation of the abdomen.

*Influenza.*—Underhill and Ringer (1920) showed that lung edema in this condition acted much as did war gas poisoning. Erythrocyte counts to 9,000,000 and hemoglobin values to 140 per cent were noted. Even in ordinary lobar pneumonia the local loss of fluid may be of importance, even if it is not the chief factor. This has been emphasized by Moon (1938). Andrews and Harkins (1937) studied the lungs and pleural fluid in twenty-three pneumonia patients. The increase in weight averaged 2.81 per cent body weight, and these authors concluded that under certain conditions this loss may be significant and, if rapid enough, may result in a shocklike condition.

*War Gas Poisoning.*—The pioneer work of Underhill (1918, 1919, 1920) has established the importance in this condition of local fluid loss into the lungs with resultant hemoconcentration and shock. Wilson and Goldschmidt (1919) and others have extended this work.

*Peptone Shock.*—The classic experiments of Simmonds (1917, 1918) showed that peptone shock and fat embolism shock differed in many important respects; in fact the effects of the latter were accomplished primarily through respiratory embarrassment. Dragstedt, Eyer, and Ramirez de Arellano (1938) showed that vitamin C does not protect against peptone shock in dogs, and Eyer, Dragstedt, and Ramirez de

Arellano (1938) also showed it to be without beneficial preventive effect in anaphylactic shock in dogs. Peptone shock in fetal dogs has recently been studied by Dragstedt, Ramirez de Arellano, and Lawton (1940).

*Constriction of an Extremity (Tourniquet).*—The paper of Wilson and Roome (1936) is of great practical value. These authors emphasized that the use of the tourniquet may be dangerous from the standpoint not only of the local gangrene but also of general shock. They showed that release of a constrictor that had been in place too long will give such a marked loss of fluid into the tissues that this cause alone will produce shock. Allen (1939) has shown that this action of the tourniquet in producing capillary damage may be prevented in part by keeping the extremity very cold while the constrictor is in place. The studies of Allen (1939) on the production of experimental shock by release of a constrictor to an extremity are of interest. This author not only has produced shock by this means but also has found that whole blood or plasma is of benefit in its treatment.

No review of recent work on shock would be complete without reviewing the recent work of Allen (1937-1939) on the temperature factor in the use of the tourniquet. This author repeated and confirmed the conclusions of Wilson and Roome (1936). He showed that there are two factors in the causation of secondary shock on release of a tourniquet: (1) the length of time of ligation and (2) the amount and nature of the tissue ligated. In man fatal shock is known to result from constriction of the thigh for an uncertain time. Blocking of the circulation of the upper arm has also caused fatal shock upon release after a very long time. This is the smallest mass of peripheral tissue known to produce fatal shock by ligation and later release. Reasoning from analogy with experimental animals, Allen (1938) concluded that a tourniquet below the elbow could not give rise to fatal shock regardless of the time before release.

Allen did a large number of tourniquet experiments on rats, developing a standardized technique whereby in a large series of animals the relation of time of constriction to development of local necrosis or generalized shock could be plotted. This not only gave interesting information in itself, but furnished a standard method for future quantitative shock experiments. At room temperature the leg tissues were found to withstand a constriction of over fifteen hours. The most interesting point about Allen's work, however, is that as the temperature was progressively raised the effects of asphyxia were accelerated as regards production of both local gangrene and systemic shock. Contrariwise, when the temperature was reduced, these effects were retarded. Near 0° C. recovery was possible after ligation for fifty-four hours. Furthermore, when a poison, such as strychnine, was introduced into a limb, a suitable series of treatments with tourniquet and refrigeration allowed the animal to tolerate many times the fatal dose without harm. These experiments

have important implications not only for the subject of shock, but also for a myriad of other surgical problems including local infection, gangrene, amputation, etc.

Allen concluded: "A temperature slightly above 0 degrees C. in a limb reduces the metabolism of the tissues so as to enable them to withstand absence of circulation for hours or even days. . . . It is believed that this principle has definite applications in practical limb surgery."

*Intestinal Strangulation.*—Studies indicate that in all types of intestinal obstruction shock is liable to result from fluid loss. In strangulation obstruction this is particularly due to local loss of plasma and blood. The paper of Scott and Wangenstein (1932) is one of the earliest reports of the importance of local fluid and blood loss in experimental intestinal strangulations and their relationship to the degree of shock present. Elman and Cole (1932 and 1934) found a similar important local fluid loss in acute portal obstruction. Aird (1935) demonstrated the importance of blood loss in strangulation obstruction. Aird and Henderson (1937) showed that there is a moderate amount of histamine in the peritoneal transudate from strangulated intestinal loops. Knight and Slome (1936) studied the amount of fluid loss in strangulation obstruction and ascribed to it an important but only accessory role. In a later paper (1937) Knight attributed a toxic role to depressor substances contained in the peritoneal exudate. Later work of Maycock (1938) indicated that these products were toxic, but not markedly lethal, and hence of little importance in the picture of strangulation obstruction. The article of Scott (1938) dealing with experimental strangulation obstruction emphasizes the role of blood and plasma loss in such cases. Scott found little evidence for either direct or transperitoneal absorption of "toxic products," except terminally. He concluded: "Whole blood and plasma are apparently lost from the general circulation in quantities sufficient in themselves to account for the symptoms of shock and death which occur in most cases of strangulation obstruction" and "when venous occlusion predominates the loss of whole blood is the chief factor, and when arterial occlusion predominates the loss of plasma is important." The anemia found by Scott following venous obstruction differs from the observations of Harkins (1937) on venous mesenteric thrombosis in human beings where marked hemoconcentration was likely to occur. Fine, Fuchs, and Gendel (1940) reported that in dogs decompression of the distended small intestine retards or prevents the progressive and eventually fatal loss of plasma that they found to result from distention. Fine, Hurwitz, and Mark (1940) also found a marked plasma loss in acute intestinal obstruction.

*Mesenteric Vascular Occlusion.*—Mesenteric vascular occlusion may be divided into four chief clinical types: (1) portal vein thrombosis, (2) mesenteric vein thrombosis, (3) mesenteric artery occlusion usually

embolic in origin, and (4) intestinal strangulation in which both veins and arteries are occluded. Experimental workers have shown that obstruction of these vessels is accompanied by an effusion of blood and bloody fluid into the peritoneal cavity, into the tissues supplied by the vessels in question, and into the lumen of the involved gut. This effusion has been found large enough, in many instances, to account for death of the animals on the basis of secondary surgical shock. Few clinical reports of the relation of such bloody effusion to resultant shock and death were found in the literature. The reports of Harkins (1936, 1937) on a study of nine cases indicate that such an effusion may be important clinically. An analysis of these cases showed that in most instances there was a plasmalike effusion into the peritoneal cavity with concomitant hemorrhagic infarction of the involved bowel. However, the blood and blood pressure studies and analyses of the peritoneal fluid in the early cases were inadequate to determine the amount of plasma and blood loss. After the study was begun, one case of fatal venous thrombosis with infarction of 240 cm. of intestine was more carefully investigated. There was extensive loss of several liters of bloody fluid into the involved bowel, peritoneal cavity, and from the stomach by vomiting with marked blood pressure fall and hemoconcentration (hemoglobin 143, hematocrit 61). The peritoneal exudate was chemically similar to blood plasma. A study of these cases indicated that effusion of circulating blood fluids may be a factor in the production of surgical shock and resultant death in patients as well as in laboratory animals. Boyce and McFetridge (1935) studied the importance of shock in mesenteric vascular occlusion and Boyce, Lambert, and McFetridge (1935) investigated it in experimental occlusion of the portal vein. The importance of local blood loss in these two related conditions was stressed. Aird (1938), using the vital red method of determining blood volume, noted a marked decrease in experimental strangulation where the veins were occluded.

*Peritonitis.*—The importance of shock in this condition has been pointed out by Moon (1938) and others. Harmon and Harkins (1934, 1937) made a study of the vasodepressant substances present in the peritoneal fluid. In 1935 they found no reduction in the bleeding volume in the shock state that accompanies acute experimental colon bacillus intoxication, and hence classified the condition as primary shock. In all types of peritonitis local fluid loss is of importance, but especially is this true of bile peritonitis as shown in the following section.

*Bile peritonitis.*—Mason and Lemon (1931, 1932) pointed out that dehydration might be an important factor in death from liver autolysis. Previous ideas concerning death in this condition and in bile peritonitis had centered around the toxic and the anaerobic bacterial theories. In a series of five papers Harkins, Harmon, Andrews, and Hudson (1935,

1936 and 1937) studied the exudate in experimental bile peritonitis and found it to be plasmalike in composition. This indicated the possibility that not merely a dehydration, but an actual shocklike condition might be a lethal factor. This was borne out by the finding of the exudate in appreciable amounts (2.2 per cent body weight) with associated blood pressure fall, hemoconcentration, and decrease in the bleeding volume. While the shock due to local fluid loss was not considered to be the entire explanation of death, it was considered to be important. In liver autolysis peritonitis the role of anaerobic bacteria seemed to be more important. These findings concerning bile peritonitis have since been verified by Manson and Eginton (1938). These latter authors also concluded that "secondary shock from loss of fluid from the vascular system" is of importance. Unfortunately, this work has not as much practical value as would appear, because human bile is much more dilute and hardly irritating enough to duplicate the shock syndrome found by Harkins and his co-workers in dogs. Hence, this experimental work cannot be applied to patients without reservations. Blalock (1935) found gastric juice less irritating to the peritoneal surfaces than bile. Using dog bile or bile salts, Andrews, Harkins, Harmon, and Hudson (1937) found that a similar shock syndrome to bile peritonitis was produced by the subcutaneous injection of bile. There was local plasma exudation and general hemoconcentration, etc. Davis (1940) found that shock resulted from subcutaneous hypertonic (25 per cent) saline injections much the same as that following Harkins, Harmon, and Hudson's subcutaneous bile injections. However, while the bile produced an outflow of plasmalike fluid, the salt produced a much more aqueous edema.

*Peritoneal Irrigations.*—These have already been considered in the experimental portion of this paper. Doménech-Alsina (1932) produced shock with hemoconcentration and oligemia by means of peritoneal irrigations of hypertonic solutions. Perla and Sandberg (1939) showed that intraperitoneal glucose produces a rise in serum potassium.

*Peritoneal Cooling.*—Mahoney (1938) induced shock by placing often renewed cold saline packs between the folds of the mesentery of anesthetized dogs for a period of one to one and one-half hours. A decrease in blood pressure, blood volume, and especially plasma volume, and total circulating albumin occurred. Only a slight blood concentration resulted and the author presented no definite evidence to explain the site of the lost plasma.

*Trauma to the Intestines.*—Blalock (1931) was the first to demonstrate the true importance of local fluid loss in this condition. In a series of twelve dogs the average loss was 4.48 per cent of the body weight. Red cells constituted only a small part of the fluid that escaped from the peritoneum covering the intestines. Storek and Ochsner (1936) also noted a fall in blood pressure following experimental intestinal

stripping. Swingle and Parkins (1935) did not agree with previous workers that shock could be produced by intestinal stripping. They found that "even two and one-half hours of vigorous stripping of the entire length of the small intestine between the fingers does not induce shock, nor significant lowering of the arterial pressure." Schachter and Huntington (1940) found that dogs given oral desiccated thyroid went into shock much more easily following intestinal manipulation than normal dogs.

## VI. THERAPY OF SHOCK

This most important aspect of the subject has been much clarified within the past few years. The rationale of empirically proved remedies has been studied, and a trend away from symptomatic treatment has been noted. For purposes of simplification, treatment will be divided under four heads: (1) standard or empirical treatment, (2) fluids, (3) oxygen, and (4) adrenal cortical extract.

1. **STANDARD TREATMENT.**—This includes remedies arrived at empirically, some of which are logical, while others should be discarded.

a. *Rest and Quiet.*—As with many treatments, this has a different rationale according to what theory one ascribes. Thus, it will prevent noiceptive stimuli; it will prevent squeezing toxins out of injured parts; or it will prevent continued bleeding and local fluid loss. No matter what the theory, rest and quiet are advisable.

b. *Elevation of Feet.*—In all cases of shock or impending shock this seems to be advisable, precaution being taken that respiration is not interfered with. Selby (1940) advised inversion of the patient as a first-aid measure in shock. In the hospital the foot of the bed should be raised and in the open the plan can be applied most simply by the stretcher bearer at the foot carrying the handles of the stretcher on his shoulders, while the rear stretcher bearer suspends the head end at full arm's length. Howat (1940) and Seldon (1940) also advised elevation of the feet as an emergency measure in counteracting shock.

c. *Warmth.*—The importance of cold in the initiation of shock was shown by the Shock Committee during World War I, by Blalock (1934), and Harkins and Harmon (1937). Warmth, then, certainly seems advisable, but too generalized heat of too high a degree might precipitate a too sudden capillary dilatation. In Cologne, at the University Surgical Clinic, Hilgenfeldt, the assistant of von Haberer, advises against too great heat for this reason in burn shock. The new electrically heated cage ("Restor" shock cage) recently described in the *Lancet*<sup>670a</sup> is of interest.

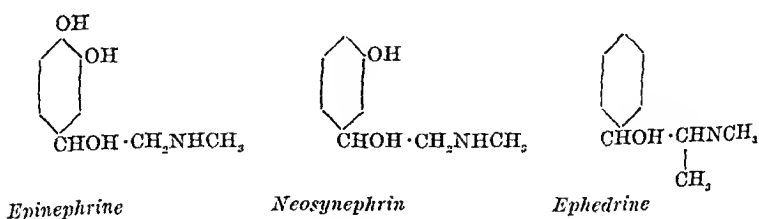
d. *Sedatives.*—These were advised by those who propagated the nervous theory, but as long ago as 1922 Cannon warned against too free a use of morphine in shock. Morphine is apt to exaggerate any anoxia that is present. The recent paper of Blalock and Cressman (1939) has

exploded the idea that spinal anesthesia is of benefit in shock. The type of general anesthesia to be used also depends on the cause of shock. Because ether was said to be harmful in histamine poisoning, adherents of the histamine theory advised nitrous oxide-oxygen anesthesia. In the presence of anoxia this latter would seem to be a poor choice.

e. *Stimulants*.—The use of stimulants would seem to be mainly symptomatic and contradictory to the use of sedatives. It is possible, however, that caffeine might be helpful in anoxia.

f. *Vasopastics*.—A perusal of the work on production of shock by adrenalin alone, discussed in a previous section, would certainly make one hesitant in using that drug in the treatment of shock. Especially is this true when it is realized that there is already a vasoconstriction present. The use of adrenalin, as advised by Guthrie (1917) and others and opposed by Atehley (1935) and others, arose because of the false concept that the peripheral arteries were relaxed in shock. In the blood pressure fall accompanying spinal anesthesia this is true, but not in real "secondary shock." Hence the use of adrenalin should be abandoned in true shock.

Despite the experimental evidence against use of the vasospastics in shock, they will be tried empirically until the objections are more definite. Johnson in 1930 advised the use of ephedrine sulfate and in 1937 suggested the use of neosynephrin hydrochloride in the treatment of acute shock from trauma and hemorrhage. So far no experimental evidence has been brought forth against the use of this latter compound. Its structural formula closely resembles that of epinephrine and ephedrine as shown by the following:



A usual dose of 5 mg. of the drug was given subcutaneously to six patients in shock, five of whom recovered. In several cases the dosage was repeated. Although the results in this series were good, the type of patient varied considerably, and adjuvant treatment with blood transfusions was used in two cases. It therefore seems that a larger series should be studied before the drug can be advised routinely. Wood (1939), of Melbourne, also used neosynephrin with good results. He advised it in conjunction with an intravenous drip of large amounts of glucose saline solution and blood transfusions.

Even some writers who heartily advocate the use of neosynephrin hydrochloride in maintaining blood pressure during spinal anesthesia

recognize that this does not mean it is applicable to secondary shock. Thus, Silvers and Leonard (1940) state that "neosynephrin . . . is not effective in cases where there is loss of blood volume or shock caused by toxic conditions such as peritonitis."

In Germany where the treatment of shock is still symptomatic in many clinics, two tyramine derivatives, veritol and sympatol, are used extensively. Sympatol is obtained from tyramine by the addition of a methyl and hydroxyl group, while veritol is obtained by adding two methyls. Thus, these two compounds are quite similar to adrenalin in their action. Reports on the action of veritol in shock were made by Büssemaker (1938), Herkel (1938), Parade (1938), Cobet (1938), Baron (1938) and Kalk (1938). Colombi, of Milan, favors veritol plus normal saline solution in shock therapy. Devine (1939), of Melbourne, has also used veritol in shock. In a small series of cases only two out of ten consecutive patients failed to respond to its administration with a rise of blood pressure of over 20 mm. of mercury.

Kunkel, Stead, and Weiss (1939) found that paredrinol ( $\alpha$ -N-Dimethyl-p-Hydroxyphenethylamine) may be of aid in some types of blood pressure fall, but that in the type of shock resulting primarily from loss of fluid from the blood stream the drug is of little value and may even be harmful.

Dodd (1940) has recently reviewed the effects of various drugs used in surgery to raise blood pressure. His remarks can be summarized as follows:

1. *Coramine*: "No effect whatever is produced on the blood pressure, nor has any other benefit been observed."

2. *Adrenaline*: "Adrenaline is regarded as useless for the purpose of raising and maintaining the blood pressure in surgery."

3. *Icoral*: "Too powerful for surgical purposes."

4. *Eserine*: "Found to vary."

5. *Ephedrine*: "Duration of the raised level is uncertain. . . . remained the chief remedy until something better was found."

6. *Cortin*: "Effect was inconsistent."

7. *Veritol* ( $\beta$ -p-oxyphenyl isopropylmethylamine): "Of the drugs so far tried it is the most satisfactory for raising the blood pressure." This drug can be given intravenously, intramuscularly, or both. Intramuscular dose is 0.75 to 1.0 c.c., rise begins in 3 to 5 minutes, maximum in about 20 minutes, duration 20 to 40 minutes, after which it should be repeated. Intravenous dose is 0.25 c.c.; rise is instantaneous and duration is 20 to 25 minutes. Combined technique of 0.75 c.c. deep into shoulder muscles and 0.25 c.c. intravenously gives immediate and maintained pressure rise for 30 to 45 minutes.

8. *Cardiazol and Veritol*: "An effective twin injection."

9. *Hypertonic Saline*: Useful in bringing up low blood pressure due to spinal anesthesia.

In a recent editorial in the *Lancet* (2: 813, 1940) data are reviewed which indicate that veritol ( $\beta$ -*p*-oxyphenyl isopropylmethylamine, an isomer of ephedrine) has no markedly superior action over other and older sympatheticomimetic drugs. In this editorial the statement is made that "experience has shown that physicians of the Continent tend to be unduly optimistic about the value of new drugs."

Freeman, Freedman, and Miller (1940) tested the effects of prolonged adrenalin injections in normal dogs without anesthesia. They used practically the same dose per minute as Gregersen and Pinkston (1936) and Hamlin and Gregersen (1939), who found no marked change in plasma volume. Freeman and associates, however, continued their injections for at least one hour to one and one-half hours and to this they attribute their finding of a definite decrease in plasma volume and a state of shock (Gregersen and co-workers continued their injections beyond 30 minutes in only a few cases). Post-mortem studies suggested that the fluid lost from the circulating blood in shock is distributed through the tissue spaces and that some of it passes through the intestinal mucosa into the lumen of the digestive tract.

2. BLOOD SUBSTITUTES.—This part of the treatment is in reality the *sine qua non* of modern shock therapy. It is not a symptomatic treatment; it attempts to get at the underlying pathology and replace what is actually lost. Four avenues of administration are available: oral, rectal, subcutaneous, and intravenous. Of these only the latter is sure enough to permit a patient's life to depend upon it. Because of difficulty in getting in the collapsed veins in shock, physicians should not hesitate to cut down on veins in case of necessity.

*Oral Fluids.*—The interesting experiments of van Liere, Northrup, and Vaughan (1940) indicated that oral administration of fluids during the acute phase of recovery from severe hemorrhage is not of material assistance to the organism as far as immediate restoration of blood pressure is concerned. Amounts of saline solution placed in the intestines of dogs did not restore blood pressure even though they were absorbed, while the same amounts of fluid given intravenously brought about distinct improvement. Orojejunal feeding has recently been used by Ravdin, Stengel, and Prushankin (1940) as a means of controlling hypoproteinemia in surgical patients. The importance of hypoproteinemia in the production of nephrotic edema was demonstrated experimentally by Leiter (1928, 1931). In the first publication he stated what is now common knowledge, that "edema usually begins when the plasma proteins have fallen to 3 per cent or less."

These methods, however, essentially involve maintaining nutrition of surgical patients and, important as they are in themselves, are not directly applicable to the emergency treatment of shock cases. There,

the intravenous administration of fluids is the best method. The new cellophane intravenous set developed by Hartman (1940) may solve some of the problems of administration of fluids and prevention of the reactions therefrom. The technique of fluid administration was presented by Gallie and Harris (1930).

*Intramuscular Fluids.*—The intramuscular injection of fluids has been used by Billimoria and Dunlop (1940) in the Department of Surgery at the British Postgraduate Medical School. The needle is inserted in the lateral surface of the thigh and usually normal saline solution or 5 per cent glucose in amounts up to 5 liters in one day is given. In more than twelve years' experience no instance of infection has occurred.

*Proctoclysis.*—This method is too uncertain and too slow for use in serious shock cases. Furthermore, Pernsse (1932) has shown that, while proctoclysis is useful for water administration, crystalloids are not well absorbed, the use of 1 per cent glucose (thus definitely hypotonic) being the best substance to give in this manner.

*Temperature of Injected Solutions.*—The popular idea that intravenous solutions should be warmed to body temperature probably originated from data observed before the importance of pyrogens was discovered (1923). More recently, De Gowing, Hardin, and Swanson (1940) have concluded that with blood, at least, it is safer not to prewarm, and that any parenteral fluids are just as safe at room temperature as when prewarmed.

*Intra-Arterial Injections.*—Davis (1937) reported good results in the treatment of experimental shock with the intra-arterial injection of hypertonic solutions. The intra-arterial injection of 5 to 10 c.c. of a hypertonic solution resulted in an elevation of the systolic blood pressure from 10 to 50 mm. Hg, this pressor response lasting from one to three hours. The arteries used were the femoral or brachial. Twenty-five per cent gum acacia was the most effective solution; whereas, 30 per cent gum acacia was one of the least effective. Control injections of isotonic sodium chloride did not increase the blood pressure. Intravenous injections produced no pressor response nor did intra-arterial injections following spinal cord section. In fact, in shocked animals the depressor response to the intravenous injection of hypertonic solutions was quite striking and might have proved dangerous. Bilateral adrenalectomy did not completely abolish the response. The response was believed to be nervous in origin. At first it was thought that removal of fluid from traumatized areas might be responsible for the pressor rise, but later it was shown that this was too slight to be a major factor. Davis concluded that: "Intra-arterial administration of hypertonic solutions is of value, inasmuch as the elevation of blood pressure is accompanied by a more adequate blood flow to the vasomotor and respiratory centers as

evidenced by the disappearance of Traube-Hering waves and dyspneic respirations." At this time Davis suggested this method for possible clinical trial, cautioning that his own experimental work was still in progress. Kendrick and Wakim (1939) corroborated the findings of Davis and his co-workers on the immediate beneficial effects of intra-arterial hypertonic saline injection. The permanent effects were harmful, however, and "death appeared to be hastened rather than delayed by the injections." Kendrick (1939) found that with 5 per cent glucose even the temporary benefits were greater after intravenous administration.

*Intravenous Amino Acids.*—Although these may be of little value in the treatment of shock, they may be of marked prophylactic value in hypoproteinemic cases, according to Elman and Weiner (1939). As Elman (1940) has shown, an average-sized blood transfusion contains only about 17 Gm. of plasma proteins and thus even several transfusions can hardly maintain protein balance, let alone restore a deficiency. Elman reported excellent results in most of a series of twenty-five patients treated with hydrolyzed casein which contains all of the eleven essential amino acids. Jejunal feeding has also been used to restore the plasma proteins. In another paper (1940) Elman pointed out that, since the serum globulin concentration and relative red cell volume both decreased following experimental intravenous injection of enzymic hydrolysate of casein, they were led to infer that the increase in serum albumin concentration was due to a regeneration.

*Recent Experimental Work.*—The work of Stanbury, Warweg, and Amberson (1936) on total plasmapheresis is of great interest. They found that the blood plasma could be almost totally removed from the blood vessels of cats and dogs, without injury to the animals, if the normal blood is replaced by a solution of 6 per cent gum acacia in Ringer-Loeke solution in which are suspended washed red cells of the same species (30 to 40 per cent). This substitution was accomplished by alternate bleeding from and injection into the carotid artery. The plasma proteins could thus be reduced to the very low level of 0.05 to 0.15 per cent. No signs of shock or of capillary dilatation or edema appeared after such "total" plasmapheresis. The blood pressure was maintained and some animals recovered and lived for indefinite periods. These authors concluded that the plasma proteins have only a physical function. Further studies of total plasmapheresis in dogs were made by Etteldorf, Mitchell, and Amberson (1937).

These observations are hardly more interesting than those of Amberson and his associates Flexner, Steggerda, Mulder, Tendler, Pankratz, Laug, Webster, and Engel (1934). These authors replaced blood with hemoglobin-Ringer solution and, while the animals did not survive permanently, they lived twenty-four to thirty-six hours. Such animals,

even though they can move around, seem dazed mentally and will neither eat nor drink. Death seems to result because the kidneys are permeable to the solution and it eventually is excreted. But that these animals can exist at all with no signs of shock with a red count of about 100,000 is indeed remarkable.

The authors conclude: "The experiments throw light upon the significance of the mammalian red corpuscles. These are important (1) in maintaining hemoglobin in the reduced state, electrochemically speaking, and (2) in holding it within membranes impermeable to it so that it cannot leave the blood stream."

Other experiments indicated an almost normal oxygen consumption of these practically "erythrocyte-free" animals. All of these results are summarized in Amberson's extensive review of blood substitutes (1937). His observations are of great theoretical interest, but, in addition, have valuable implications concerning shock and its treatment.

The fluids that are available for intravenous use are included in the following list:

- a. Water
- b. Crystalloids, saline crystalloids (normal salt solution, Ringer's solution, Locke's solution), glucose
- c. Acacia
- d. Ascitic fluid
- e. Whole blood (also red cell concentrate and hemoglobin-Ringer solution)
- f. Plasma

With the exception that the use of ascitic fluid is still in the experimental stage, these six types of fluid are listed in approximate reverse order of preference. In discussing the relative inefficiency of crystalloids in the treatment of shock due to hemorrhage, Buttle, Kekwick, and Schweitzer (1940) concluded that plasma is the only effective blood substitute, at least so far as their experiments on cats were concerned. The other substitute solutions they placed in the following descending order of value: serum, hemoglobin-Ringer, gum-saline, red cells in crystalloid solution, isotonic saline, isotonic glucose.

a. *Water*.—The prevention of dehydration in surgical patients is important in preventing shock. The important studies of Coller and Maddock and their associates are of prime importance in this regard. Not only are these studies of interest from the prognostic standpoint, but they have led to a more adequate conception of the fate of crystalloid solutions in the body. In this regard papers include those of Miller and Poindexter (1932); Marriott and Kekwick (1937); Coller, Bartlett, Bingham, Maddock, and Pedersen (1938); Bartlett, Bingham, and Pedersen (1938); Winslow (1938); Bartlett (1939); Fuge and Hogg (1938); Nelson (1939); Elkinton, Gilmour, and Wolff (1939); Drew,

Seudder, and Papps (1940); King (1940); Emhardt (1940); Lands, Cutting, and Larson (1940); and Maddock and Collier (1940). Walter (1940) discussed the proper preparation of parenteral fluids so as to eliminate pyrogens.

The importance of dehydration as a factor in secondary shock was stressed by MacFee and Baldrige (1934), who presented data on infusions of saline solution and the effect on shock. Fuge and Hogg (1938) have also studied the question of postoperative fluid balance. They found that in a series of twelve surgical patients the average insensible fluid loss per day was 1,460 Gm. with extremes of 1,150 and 1,830 Gm. per day. The insensible loss for all cases averaged 39 per cent of the total output. It seemed to vary more with the size of the patient than with the type or extent of the operative procedure. Latimer (1939) has recently summarized the work of others on water balance and added a practical working scheme of his own. The importance of such a plan in the pre- and postoperative period will go far in the prophylaxis against shock. Recent reviews of the subject also include those of Mason and Hellbaum (1938) and Darrow (1940).

The work of Cutting and Koppányi (1938) and of Cutting, Larson, and Lands (1939) is of interest in showing how large amounts of fluid can be tolerated by normal animals. Using cats they found that the following doses were tolerated:

Normal saline	5.1 c.c. per minute per kilogram
	706 c.c. total per kilogram
	≡ 350 c.c. per minute or 50 L. total
	in 2½ hr. for average-sized man
5 per cent glucose	4.2 c.c. per minute per kilogram
	465 c.c. total per kilogram

Swingle, Parkins, Taylor, and Hays (1937) showed that considerably less than this amount of fluid, when given in the form of distilled water, would lead to death in dogs.

b. *Crystalloids, Salt Solution, and Glucose Solution.*—The reports of Hoitink (1935, 1938), of Utrecht, Holland, are almost solitary in favoring crystalloid solutions over blood transfusion. He found in his experiments that none of the infusion liquids gave better results than 0.9 per cent sodium chloride solution. He concluded that after an acute dangerous hemorrhage its use is "preferable to the use of other artificial blood substitutes and to blood transfusion."

A careful perusal of Hoitink's papers reveals the following important fact. He does not state how rapidly the blood was withdrawn, except to say that it was taken from the carotid artery by means of a large cannula, and he makes no mention of the removal being intermittent. So it may be assumed that he was dealing with a rapid hemorrhage. The

quantity of the hemorrhage was large, averaging 5.6 per cent body weight. As to the interval before injection of the blood substitute, his only remark is that it is done "shortly afterward." Thus, this author was dealing with cases of hemorrhage pure and simple which may have been so sudden that there was no time for the irreversible vascular wall changes of shock to occur. In such a case even the advocates of the generalized capillary permeability theory of shock would not expect such an increased permeability. With the normal saline solution to preserve the blood volume and pressure, such animals should remain alive almost as well as patients with marked chronic anemia. Experiments such as Hoitink's may be, therefore, an example of the danger of applying ideas obtained from hemorrhage experiments to shock treatment. Hemorrhage that has been allowed to remain untreated so long that shock is present is, of course, a different matter. Simultaneously with Hoitink's report, Konrich (1935) arrived at exactly the opposite conclusion on the same material, finding that sodium chloride solution is inferior to all others. Neuwelt, Neeheles, and Levinson (1940) also found experimentally that whole blood or plasma was markedly superior to saline solution in treating shock.

Despite these objections, salt solution has some place in shock treatment when one remembers its limitations. Lamb (1910) advised intravenous saline solution with the head of the patient lowered. Pilcher and Sollmann (1914) had early shown that saline infusions give an increased tone to the vasomotor center, both before and after hemorrhage. Cutter (1936) presented data on the effects of large volume intravenous injections, and Cutting, Lands, and Larson (1938) studied massive saline infusions experimentally. The dangers of giving isotonic crystalloid solutions too rapidly have been worked out in considerable detail by Gilligan, Altschule, and Volk (1938) and by Gilligan, Altschule, and Limenthal (1938). Sessler (1940) believes that saline solution has another virtue: The contained sodium relaxes the smooth muscle of the constricted arterioles. The relaxing effect of salt on constricted vessels was first shown by Roy (1884).

*Hypertonic Solutions:* These have long been advised because it was thought that their viscosity more nearly resembled plasma and because of their osmotic action. Both of these virtues are apt to be evils at the same time and in dehydration hypertonic solutions may increase the blood volume at the expense of the all-important cell water. Murphy, Correll, and Grill (1941) in studying the effects of intravenous solutions in patients with and without cardiovascular defects observed dangerous reactions after the use of 50 per cent glucose solution.

*Glucose:* Except as a nutriment and protection for the liver, glucose seems to have little advantage over salt solutions in shock treatment. The value of intravenous glucose injections in shock was shown by Erlanger and Woodyatt (1917).

*Danger of Excess Use of Crystalloid Solutions:* This aspect of the treatment of shock has received considerable attention of late, but the series of six articles published by Blalock and his associates in 1932 and 1933 remains the most complete exposition of the subject. Beard and Blalock (1932) studied the composition of the blood during continuous trauma to the intestines when no fluid was injected and when fluid was injected continuously. They found a great decrease in the absolute value of total plasma protein in circulation following injection of normal salt or glucose solution, while blood did not give this effect. Blalock, Beard, and Thuss (1932) obtained similar results in dogs in which the blood pressure was low for unexplained reasons. They even found, when whole blood or serum was injected, if deductions were made for the protein present, in that injected whole blood or serum a great decrease in the absolute amount of plasma protein was found. The findings of Beard, Wilson, Weinstein, and Blalock (1932) and of Blalock and Beard (1932) on saline injections in experiments on trauma, graded hemorrhages, histamine injection, and spinal anesthesia were essentially the same.

Beard, Wilson, and Blalock (1933) found that, in the presence of low blood pressure produced by histamine or graded hemorrhage, subcutaneous or intraperitoneal normal saline solution would produce a decrease in the absolute amount of plasma protein. On the other hand, similar saline solution introduced by stomach tube produced no such effect. Blalock, Wilson, Weinstein, and Beard (1933) found that the introduction of pituitary solution or epinephrine did not prevent the loss of protein from the circulation in cases where normal saline solution was administered intravenously.

These ideas were extended by other writers. Horsley (1934) noted that normal salt solution escapes readily from the vessels in shock. Davis (1936, 1937) also showed that crystalloid solutions may be harmful in certain cases of shock.

In this regard it is interesting that Krogh stated (1922) in his well-known monograph on the *Anatomy and Physiology of Capillaries*: "Injections of isotonic and hypertonic solutions of various crystalloids have been exhaustively tried, but found to be useless, and it is easy to see that in cases where the permeability of the capillary wall is increased, such solutions must leave the circulation very rapidly."

Hepler and Simonds (1938) performed other experiments indicating the rapid loss of crystalloid solutions injected during shock. Shock was produced by impounding the blood in the liver and intestinal tract by means of temporary hepatic vein ligation. Injection of normal saline solution in quantities up to somewhat more than the estimated initial blood volume induced a rise in systemic pressure during the injection, but the pressure fell almost to the previous low level within from one to three minutes after the injection was stopped. They concluded: "The

rate of fall in blood pressure and reduction in blood volume after injection of salt solution under the conditions of these experiments indicates the rapidity with which fluid escapes from the circulating blood." At another point they stated "the use of such fluids is definitely contra-indicated in shock." In their dogs, which received a large injection of saline solution, a surprising amount of fluid was found to have escaped into the lumen of the stomach and into the gastric submucosa.

c. *Acacia*.—Good, Mugrage, and Weiskittel (1934) stated: "Acacia is the dried gummy exudate of the stems and branches of *Acacia Senegal* or of some of the other species of *Acacia*. It is an inert polysaccharide of high molecular weight having an acid nucleus. It is related to the dextrans, glycogen, starch and cellulose. Like the latter it is amorphous, odorless, translucent, and on hydrolysis yields one or more sugars, generally pentoses and hexoses." The viscosity of a 6 per cent solution is much the same as plasma. The solution is somewhat acid. Analysis shows 0.5 per cent total nitrogen, which may explain some of the anaphylactoid reactions observed.

Use of colloid solutions intravenously was first made by Czerny (1894), who infused protein and acacia solutions into experimental animals. Hogan (1915) made the first clinical use of these substances, injecting 2.5 per cent gelatin solution. Gum acacia was first used clinically by Hurwitz (1917), who, stimulated by Hogan's (1915) earlier use of gelatin-saline solution, successfully treated the first cases in San Francisco in 1916. Soon, largely because of the interest of Bayliss, gum acacia was used extensively at the Western Front. The Base Hygiene Laboratory of the B.E.F. at Boulogne was soon producing 75 liters of sterile gum solutions daily (Telfer, 1919). Lack of experience with proper preparation caused some failures. For a discussion of the early development of this solution the reader is referred to the almost incomparable review by Amberson of blood substitutes (1937).

Following its use in World War I, acacia enjoyed wide popularity, especially in Great Britain and at the Mayo Clinic. White and Erlanger (1920) used it experimentally. Hancock (1938) favored it. Tui, Schrifft, and Ruggiero (1939) showed that most of the toxic reactions of acacia may be due to contained pyrogen. The use of acacia in war has been recently reviewed in correspondence (1939) in the *Journal of the American Medical Association*.

Maytum (1932) reported that in a series of approximately 3,000 intravenous injections of acacia solution given at the Mayo Clinic, only one anaphylactoid reaction occurred. This was in the only patient in whom multiple injections were separated by a long enough interval to develop hypersensitiveness. In experiments on nineteen sensitized guinea pigs, seven developed severe anaphylaxis with two deaths. It was concluded that acacia is a mild antigen, and that under rare circumstances a patient may exhibit anaphylactic symptoms when a previous dose has been ad-

ministered some weeks or months before. It seems from this work of Maytum's that acacia should never be given longer than a week after the last previous and possibly sensitizing dose.

Good and Mugrage (1934) analyzed the results of administration of acacia to 111 patients in three private hospitals, 53 per cent of these patients being surgical. Most of the others suffered traumatic injuries or shock after ruptured ectopic pregnancy, etc. The dosage of acacia varied from 100 to 1,700 c.c. and 77 patients survived, a mortality rate of 30.6 per cent. Twenty-four of the patients who recovered and 6 of those who died received blood transfusions in addition to the acacia. Acacia alone raised the systolic blood pressure an average of 35.5 mm. Hg. The minimum rise was 12 mm. and the maximum rise 70 mm. Hg. In most cases the pulse rate after the injection of the gum acacia solution was lowered 10 to 20 beats per minute. In 4 instances the rate was lowered 40 to 55 beats per minute; in 8 there was no change. There were no true anaphylactic reactions, although minor disturbances, including vomiting, headache, or chills, occurred in 11.7 per cent of the cases. None of the deaths in the entire series could be attributed directly to either the gum acacia or blood transfusions.

Good and Mugrage concluded: "A colloidal solution like 6 per cent gum acacia solution is preferred to any of the crystalloidal solutions for raising and maintaining the low blood pressure of surgical shock. It is safe, ready, and inexpensive."

A very adverse report on the use of acacia comes from the University of Iowa, where Dick, Warweg, and Anderseh (1935) found bad results attending its use in cases of nephrosis. While these conclusions may not be entirely applicable to other conditions, the extensive acacia deposits found in the liver and also in the bone marrow, lymph nodes, lungs, kidneys, and spleen would tend to make one cautious in using large amounts of acacia. Furthermore, once acacia has been given, blood counts and blood typing become difficult. Christie, Phatak, and Olney (1935), in studying the effect of acacia on the physical-chemical properties of the blood, found that it not only led to a decreased hemoglobin, but coated the red cells and interfered with their respiration. The effect of this coating in preventing accurate cross-matching of blood for transfusion is well known. In such cases either a universal donor must be used or the blood drawn for testing before gum acacia administration.

Another unfavorable report was made by Studdiford (1937), who collected several adverse accounts from the literature as well as reports of several deaths following the use of gum acacia at Bellevue Hospital. Three of the latter cases formed a group with a syndrome characterized by cyanosis, dyspnea, tachycardia, and pulmonary edema. Autopsy was performed in 2 cases and 1 of these showed an extensive destructive

lesion of the liver. In all, 6 serious reactions with 4 deaths occurred in the Bellevue series of 56 patients receiving gum acacia. Studdiford concluded that acacia may result in serious liver damage and also tends to cause serious disturbances of the erythrocytes, interfering with normal gaseous exchange, increasing the tendency to rouleaux formation, accelerating the sedimentation rate, and causing a conglutination of the red cells with the possibility of capillary blockage.

He concluded: "Hemorrhage and shock can be treated more safely by the use of the simpler saline or glucose infusions in combination with transfusion. The possibility for harm is less than with acacia solution. The only indication for the use of acacia solution intravenously in the treatment of shock and hemorrhage is as a last resort when transfusion is unavailable."

Not only is the danger of acute liver damage an important one, but the possibility of chronic acacia deposition is to be considered. Dick, Warweg, and Andersch (1935), as mentioned above, reported finding a considerable amount of acacia in the liver of a child dying some time after infusion.

It is definitely recognized that these maltoward reactions are much more apt to occur after using inferior or deteriorated samples of acacia, Bayliss (1922) stating that all reactions were due to faulty technique. The fact, however, that many of the most recent adverse reports concern reliable preparations properly administered causes one to question seriously the value of giving acacia except when blood is not available.

Hall (1938) performed experiments, concluding: "Repeated intravenous injections of gum acacia solution in dogs have resulted in evident damage for carbohydrate and serum protein metabolism functions of the liver. These changes were shown by glucose and galactose blood sugar tolerance curves and determinations of the plasma proteins. Alteration of the clotting mechanism of the blood, especially the lowered fibrinogen content, has resulted in failure to clot, or in formation of small, fragile and fibrous clots and in a longer bleeding time. The removal rate of bilirubin injected into the blood was unaffected."

Cattell and co-workers (1939) opposed the use of acacia. Saslow (1939) found the colloid osmotic pressure of samples of 6 per cent acacia in 0.9 per cent sodium chloride to vary from 246 to 260 mm.  $H_2O$  at  $20^{\circ} C$ . This closely approximates the average value for human serum of protein concentration ranging between 6 and 8 per cent which was 276 mm.  $H_2O$ .

Recent observations of Kendrick, Keeton, and Foley (1938) showed that, when an amount of 12 per cent acacia solution in 0.85 per cent sodium chloride approximating the plasma volume is injected in dogs, there is an immediate increase in blood volume (22 to 30 per cent) and a decrease in the serum proteins. The value for serum acacia plus

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points will be mentioned here. I must partially disagree with one statement in Vary's excellent article where the latter says that cadaver blood found wide usage in Moscow until 1936 when placental blood began to be used. When I visited Moscow in June, 1939, cadaver blood was still widely used, at least in the Institute Sklifassovsky (Central Emergency Hospital). The excellent review of Amberson on blood substitutes (1937) should also be consulted. Other excellent reviews of the use of blood transfusion are those of Lewisohn (1934), Fell (1938), Tuohy (1938), Grimberg (1939) (use in France), and DeKleine (1938) (use by Red Cross). The advantages of transfusions in pneumonia have been reviewed recently by Whitaker (1939), who makes a point that the danger of overloading the heart has been grossly exaggerated.

Heister (1750) suggested blood transfusions as a treatment in shock cases. John Hunter also suggested their use. Crile (1910) advised blood transfusions by the direct method in the treatment of shock. Over twenty-two years ago Blem, of Los Angeles, used to carry citrated blood to places over seventy miles away from that city, this being the first application of the stored-blood principle. Transfusions have been especially useful in preventing shock after neurosurgical operations, as reported by Bird (1929) and other authors. Transfusions have been favored by numerous writers, such as Orr (1934), W. Hunter (1935, 1937), Hume (1938), and Hamilton-Paterson (1939), to mention only a few. Another solution used by Hunter (1935), of Newcastle, had the following composition: ephedrine hydrochloride, 0.060 Gm.; glucose, 30 Gm. (or 5 per cent); gum acacia, 35 Gm. (or 6 per cent); and distilled water, to one pint. Hunter (1937) wrote considerable concerning the use of blood transfusions in obstetric shock. The increasingly important role of transfusions is shown by their popularity. At the Mayo Clinic in 1937, the number of transfusions was 2,805, and of these 36 were 1,000 c.c. or more. In contrast to these figures, during the twenty-two-year period, 1916-1937, a total of 22,937 transfusions was given, an average of a little over 1,000 a year. In 1938, 3,295 transfusions were given, and in 1939, 3,723 (Lundy, Tuohy, Adams, Mousel, and Seldon, 1940).

Various innovations in the technique of transfusions are numerous. The use of *autotransfusion* in the treatment of a wound of the heart by Watson and Watson (1936), of Pittsburgh, is an example in kind. These authors also collected all cases of autotransfusion for various conditions from American literature, finding 272 such cases and adding 2 of their own. Nonfatal reactions were reported in 9 cases (3.3 per cent) and death in 4 (1.5 per cent). The Watsons believed that the possibility of using hemolyzed blood is the chief danger rather than bacterial contamination. The technique of obtaining and administering blood as used in wartime hospitals in Great Britain has been presented by Stewart (1940), of the Royal Infirmary of Edinburgh.

protein about equals the original value for serum protein. After repeated injections, the acaemia is progressively deposited in the liver as shown by periodic biopsies, gradual increase in liver size, and tissue analyses. In one animal the liver was five times normal size, and of the 756 Gm. injected, 450 (58.8 per cent) were recovered from the liver. These authors concluded that the diminution of serum proteins is not to be regarded as an index of failure of the proteogenic function of the liver, but rather as due to a displacement of the proteins by the acaemia.

In conclusion it seems that, while acaemia may be of benefit, there are other more perfect blood substitutes. Plasma has almost the portability and storability of acaemia without its side reactions.

d. *Ascitic Fluid*.—Davis and White (1938) used human ascitic fluid in the treatment of experimental secondary shock. This work was reviewed in the current comment of the *Journal of the American Medical Association* for the same year. Choisser and Ramsey (1938) also performed experiments on the use of ascitic fluid. They produced shock in dogs by trauma, hemorrhage, or a combination of the two, and treated it with human ascitic fluid. Although they called the shock they produced "primary," this really makes little difference, as they apparently were dealing with what most other workers call "secondary" shock. Nineteen specimens of ascitic fluid were used, the majority of which were obtained from human cases of advanced portal cirrhosis. These authors stated that this fluid varied in protein content from 2.1 to 4.2 mg. per cent. They probably meant grams per cent. All fluids were found to be not only sterile but bacteriostatic. Favorable results were obtained only when fluids devoid of agglutinins were used. The effect on shock was immediate and prolonged. The amount of blood pressure rise was much the same as that obtained with whole blood. In a more recent paper, Choisser and Ramsey (1939) reported that ascitic fluid could be freed of agglutinins and rendered safe for intravenous use in relief of experimental shock in dogs, without necessity for preliminary cross-matching. They accomplished this by a process of electrodialysis, adjustment of pH, and subsequent Berkefeld filtration.

More recently Mulder, Davis, and Streeter (1939) have applied the lyophile principle to ascitic fluid. The dried ascitic fluid redissolved readily and was used in various concentrations, usually about two and one-half times the original. Cross-agglutination tests were used and the fluid administered experimentally to dogs which were in shock as a result of bleeding. The animals usually recovered with return to normal of the blood pressure and oxygen consumption. The plasma proteins fell temporarily. So far, this type of therapy has not been applied to human beings.

e. *Whole Blood*. *Blood Transfusions*.—The entire history and present status of this most important item in shock treatment have been so well outlined by Vary in his recent review in *SURGERY* (1940) that only a few

this conception so that it would be more commonly considered advisable in doing a transfusion to administer that amount of blood, whether it is 250 c.c., 500 c.c., 750 c.c., 1,500 or 2,000 c.c., so that the patient may be adequately provided with blood."

I would like to paraphrase freely a portion of the above quotation: "A standard pint transfusion is chosen more to fit the donor than the patient; an ideal adequate transfusion should be chosen to fit the patient and several donors should be used when necessary."

Lundy and associates (1938) also stated that "the results that have been obtained with the so-called massive transfusion in certain instances have been dramatic." They, however, believe that Marriott and Kekwick's system is too elaborate and devised a modified method of intermittent small transfusions. McNealy (1938) also deplored the "ritualistic" use of always a pint transfusion.

The reports of Marriott and Kekwick (1935, 1936) are of importance in that they pioneered in directing attention to the necessity for fitting the size of the transfusion to the needs of the patient. Using a visible drip with citrated blood, they avoided settling of the cells by bubbling a slow stream of oxygen through the suspended donor flask. Their cases included bleeding peptic ulcers to a large extent and they gave blood at a usual rate of forty drops per minute (130 c.c. an hour) until the anemia was controlled. The following data concerning the eighty-seven drip transfusions carried out by them at the Middlesex Hospital, London, during 1935 may be of interest:

Total number of transfusions	87
Total volume of blood drip transfused (excluding citrate)	232.5 L.
Total duration of these transfusions	2,545 hr.
Average drip transfusion	2.7 L. (= 5 pt.)
Average duration of each drip transfusion	29 hr.
Largest single transfusion	6.3 L. (= 11 pt.)
Longest single transfusion	62 hr.

In an editorial DeBakey (1938), of Ochsner's clinic, opposed the suggestion of Marriott and Kekwick concerning continuous drip transfusions. A closer perusal of this editorial indicates, however, that DeBakey merely opposed citrate transfusions in general. He favored large transfusions when necessary and has given as much as 7 liters of unmodified blood in three or four days. He practically denies the possibility of "speed shock" and has transfused "not infrequently" as much as 650 c.c. in three minutes.

*Stored Blood. The "Blood Bank":* Bureeva (1935) described the blood bank system in Leningrad at the Research Institute for Blood Transfusion under the leadership of (the late?) Prof. E. Hesse. As Fantus (1938) pointed out, the idea of calling a blood collection a blood bank and making it function like a blood bank originated at the Cook

*Transfusion Reactions:* Seed (1938) reported an incidence of 6.76 per cent reactions following the use of 1,196 transfusions of preserved blood. These could be separated as follows:

Immediate reactions (within 30 min.)	34%
Delayed reactions	49%
Jaundice reactions	11%
Urticaria reactions	6%

In about 5,000 transfusions at the Cook County Hospital 3 deaths occurred. Fell (1938) reported an incidence of 11.6 per cent reactions following the use of fresh blood in 500 transfusions at the Presbyterian Hospital, Chicago. No deaths occurred, but in another Chicago hospital 6 deaths followed 525 transfusions.

Watson and Sanders (1941) of Memphis pointed out that their transfusion reaction rate in a series of 1,600 transfusions had markedly decreased in the past few years. From 1926 to 1935 the reaction rate per transfusion was 17 per cent, while from 1935 to 1940 it was 2.2 per cent. Seldon (1941) of the Mayo Clinic has recently described a device for warming cold refrigerated blood. Stetson (1940) in his recent review of blood transfusion opposes the use of preserved blood. To prevent the occasional occurrence of urinary suppression after intravascular hemolysis following blood transfusion, Bushby, Hart, Kekwick, and Whitby (1940) of the British Army Blood Transfusion Service have several suggestions. These authors believe that suppression of urine in such cases is due to renal tubular obstruction with hemoglobin products. The conditions necessary for its prevention are a high urinary output of at least 1,500 c.c. per day and a constant urinary reaction of pH 6.4 or over. Fluids and alkalis by mouth or vein best fulfill these aims.

*Experimental studies* have been made by Iljin (1935) and Knz and Weber (1935). The Russian workers, Petrov, Filatov, Bogomolova, and Stroikova; Wesselkin, Lindenbaum, and Kartaševskij; and Mineev (1935), have studied the nature of hemolytic shock accompanying blood transfusion. They found an increase in the potassium content of the recipient's serum accompanying such reactions.

*Massive Transfusions (Adequate Transfusions):* It has long seemed to me that there is no more reason why every transfusion should be standardized at a pint than that every diabetic patient should always receive ten units of insulin. A statement by Laudy, Tuohy, and Adams (1938), from whose report the above Mayo Clinic statistics were obtained, substantiates this view. These authors stated:

"Blood transfusion has come to have a different meaning to some of us than to the average person. Previously because a donor could donate 500 c.c. of blood without untoward result, 500 c.c. as a transfusion came to be considered as a full transfusion. We would like to change

this conception so that it would be more commonly considered advisable in doing a transfusion to administer that amount of blood, whether it is 250 c.c., 500 c.c., 750 c.c., 1,500 or 2,000 c.c., so that the patient may be adequately provided with blood."

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I would like to paraphrase freely a portion of the above quotation: "A standard pint transfusion is chosen more to fit the donor than the patient; an ideal adequate transfusion should be chosen to fit the patient and several donors should be used when necessary."

Lundy and associates (1938) also stated that "the results that have been obtained with the so-called massive transfusion in certain instances have been dramatic." They, however, believe that Marriott and Kekwick's system is too elaborate and devised a modified method of intermittent small transfusions. McNealy (1938) also deplored the "ritualistic" use of always a pint transfusion.

The reports of Marriott and Kekwick (1935, 1936) are of importance in that they pioneered in directing attention to the necessity for fitting the size of the transfusion to the needs of the patient. Using a visible drip with citrated blood, they avoided settling of the cells by bubbling a slow stream of oxygen through the suspended donor flask. Their cases included bleeding peptic ulcers to a large extent and they gave blood at a usual rate of forty drops per minute (130 c.c. an hour) until the anemia was controlled. The following data concerning the eighty-seven drip transfusions carried out by them at the Middlesex Hospital, London, during 1935 may be of interest:

Total number of transfusions	87
Total volume of blood drip transfused (excluding citrate)	233.5 L.
Total duration of these transfusions	2,545 hr.
Average drip transfusion	2.7 L. (= 5 pt.)
Average duration of each drip transfusion	29 hr.
Largest single transfusion	6.3 L. (= 11 pt.)
Longest single transfusion	62 hr.

In an editorial DeBakey (1938), of Ochsner's clinic, opposed the suggestion of Marriott and Kekwick concerning continuous drip transfusions. A closer perusal of this editorial indicates, however, that DeBakey merely opposed citrate transfusions in general. He favored large transfusions when necessary and has given as much as 7 liters of unmodified blood in three or four days. He practically denies the possibility of "speed shock" and has transfused "not infrequently" as much as 650 c.c. in three minutes.

*Stored Blood. The "Blood Bank":* Bureeva (1935) described the blood bank system in Leningrad at the Research Institute for Blood Transfusion under the leadership of (the late?) Prof. E. Hesse. As Fantus (1938) pointed out, the idea of calling a blood collection a blood bank and making it function like a blood bank originated at the Cook

County Hospital in Chicago. The technique used at this institution has been described by Schirmer (1938). Exact details of blood preservation technique and conduct of a blood bank are given by Fantus and Schirmer (1938). Blood banks are called blood depots in England.

Lewisohn (1938) wrote opposing the method used at the Cook County Hospital. This author pointed out that by the technique used at that institution the patient does not receive pure blood, but blood diluted in equal parts with normal saline solution. He pointed out that such dilution is entirely unnecessary and may diminish considerably the benefit obtained in many cases. Cotter and MacNeal (1938) advised buffering the sodium citrate solutions used for blood preservation with citric acid solution. The use of bank blood was discussed by Goldstein, Olsman, and Edlin (1939). Novak (1939) found experimentally that, with the possible exception of sulfanilamide, bacteriostatic drugs are not useful in blood preservation.

Cameron and Ferguson (1939) have recently summarized their experiences with 1,000 transfusions from the blood bank of the Philadelphia General Hospital. The blood is given undiluted, contrary to the Cook County Hospital practice. It is interesting that only 25 of 1,123 deposits in the bank (2.2 per cent) were discarded because of age. The remaining 98 specimens were not used because of unsuitability (seropositive, 53; hemolyzed, 17; infected, 6; etc.). Discarding was done at five weeks, but the demand, especially for the commoner blood groups, was so great that the average flask remained in the refrigerator only five days. A total of 7.4 per cent of the transfusions had reactions.

De Gowin, Harris, and Plass (1939) studied the plasma potassium in stored blood, finding it to increase considerably. De Gowin, Hardin, and Harris (1940) studied the toxicity of blood with high plasma potassium when used for transfusion into human beings. They concluded that when given slowly such blood was not toxic and that "the concentrations of plasma potassium encountered in blood stored for one month are not high enough to cause significant increases in the serum potassium of the recipient." It is of interest, however, that all of the recipients in the cases of De Gowin and associates had normal values before transfusion. Whether this same conclusion as to the nontoxicity of high potassium blood would apply to patients already with high potassium levels is to be considered. De Gowin, Harris, and Plass (1940) extended these ideas in their comprehensive review of the use of preserved human blood.

De Gowin, Harris, and Plass (1940), of Iowa City, found that the blood preservation solution giving the least hemolysis included: ten volumes of blood, thirteen volumes of 5.4 per cent anhydrous dextrose in water, and two volumes of 3.2 per cent dihydric sodium citrate in water. At the end of a month's storage, blood in this dextrose-citrate mixture had hemolyzed only from one-twenty-fifth to one-fiftieth as much as did blood in citrate solutions alone or in citrate-saline mixtures.

*Advantage of Glucose in Preserving Fluid:* Numerous writers have found that glucose tends to preserve blood better than a simple inorganic solution. Kolmer and Howard (1940) found that blood is better preserved by the addition of dextrose (modified Rous-Turner, 1917) or of dextrin (Maizels and Whittaker, 1939, 1940) than by plain citrate or the Moscow Institute of Hematology methods. Aylward, Mainwaring, and Wilkinson (1940) and Dubash, Clegg, and Vaughan (1940) also reported that citrate-glucose seemed to be the best preservative for blood, inhibiting, although not preventing, the increase in plasma potassium. Maizels and Whittaker (1940) working at the Emergency Blood Transfusion Center, Maidstone, England, advise a more dilute mixture than that suggested by De Gowin, Harris, and Plass (1940) (*vide supra*). They think their solution is more isotonic and use a solution of sodium chloride (0.5 per cent), sodium citrate (1.05 per cent), and glucose (1.0 per cent).

*Changes in Stored Blood:* The interesting observations of Levine (1940) on the length of life of a transfused red cell in the recipient indicate one of the objections to the use of stored blood. Identifying the donor cells in the patient by means of the group specific factors M and N, he found that cells stored 3, 10, or 14 days survived for 80, 60, or 20 days, respectively, as compared with the survival time of 95 days for fresh cells. Two of the best recent reviews on the changes in stored blood are those of Bull and Drew (1940) and of Scudder (1940).

Mainwaring, Aylward, and Wilkinson (1940) found that the potassium content of plasma from two-week-old stored blood contained 116 mg. per 100 c.c. This suggested to them, as it has to others, the possibility of toxic reactions, and they advised early separation of the plasma from the blood and slow administration where high potassium plasma had to be used. The studies of the English workers, Downman, Oliver, and Young (1940) at the Emergency Blood Transfusion Depot, Sutton, also indicated an increase in potassium of stored blood. The blood was stored at 2 to 4° C. according to Medical Research Council specifications (one volume of blood to one-half volume of 1.05 per cent sodium citrate in 0.85 per cent sodium chloride). During the first week the plasma potassium concentration rose rapidly to between five to ten times the initial level; thereafter the rise was comparatively slow. The potassium came from the red cells, its liberation being quite independent of hemolysis. Macdonald and Stephen (1939) also discuss the changes in stored blood, especially the decrease in number of erythrocytes.

Quick (1940) and Ziegler, Osterberg, and Hovig (1940) reported a decrease in the prothrombin content of preserved blood. While this is of interest, it is not a serious deterrent to the use of preserved blood in shock conditions. Warner, De Gowin, and Seegers (1940) also found a decrease in the prothrombin content of stored blood, the value reaching the 50 per cent level at the end of about three weeks. Observations on

changes in human blood stored at 4° C. were made by Lipp and Hubbard (1940).

*Rate of Transfusion:* Some aspects of this subject have already been described under the heading "Massive Transfusions." In a more recent article Marriott and Kekwick (1940) stated: "In every transfusion the volume of blood to be administered and the rate of its administration should be matters of primary importance. The custom of giving a transfusion, meaning about a pint of blood in half an hour, is irrational and unsatisfactory." This particular article is devoted to a consideration of transfusion for the relief of anemia uncomplicated by hemorrhage, and for this purpose they advise adequate transfusions. Once the required rise of hemoglobin has been settled for any case, the volume of blood in cubic centimeters needed may be calculated as follows:

$$\frac{\% \text{ rise of Hb. required}}{100} \times \text{Patient's normal blood volume in c.c.}$$

The blood volume may be roughly determined as 40 c.c. per pound body weight.

Marriott and Kekwick again emphasized the importance of slow calibrated administration by the drip method that they advised five years ago (1935). In a series of massive transfusions to 177 adults, 67 of whom were over 50 years of age and 35 over 60 years of age, almost all these patients showed no symptoms of cardiac embarrassment. The average volume of blood (exclusive of citrate) given in the 177 transfusions was 2,039 c.c.; in 21 cases it was more than 3,000 c.c. All transfusions were given very slowly; the average duration was 27.1 hours, with an average rate of 84 c.c. per hour (since the average volume of citrated blood was 2,285 c.c.). The slight distress present in 5 cases quickly disappeared in 4. One of the advantages of slow administration is that, if cardiac failure does develop, there is adequate time to recognize it. The one death occurred when a transfusion was done in a private dwelling. These authors finally postulate that these slow transfusions for anemia allow time for the excess plasma to leave the blood stream. They advise that the rate not exceed fifty drops per minute for the average-sized man.

It seems that this rate limit may be desirable in chronic anemia cases but not advisable in acute shock or hemorrhage cases. If a patient has just lost 1,500 c.c. from a severed vessel, it seems hardly necessary to take nine hours to restore that blood. Theoretically it would seem that the more rapidly the blood or plasma has been lost the more rapidly may it safely be replaced, provided such restoration is begun promptly.

Marriott and Kekwick (1940) in a later note point out that, while they believe that in chronic anemia with no marked decrease in blood volume slow transfusions are necessary, in shock with lowered blood volume very

rapid transfusions may be necessary. Thus, a pint may be given in fifteen minutes or the rate may be even faster in severe cases.

*Placental Blood:* Fine, Alter, and Baptisti (1940) summarized their experiences with the use of placental blood for transfusion at the Baltimore City Hospital. The use of such blood seemed theoretically attractive, but they concluded that it was impractical, chiefly because of contamination of a high percentage of specimens.

*Red Cell Infusion:* While many articles have been written on the use of plasma, few have appeared on the subject of cell infusion. One of these latter is the paper of Beumer and Schwartz (1939) recommending the use of plasma-free cells in anemia. The use of blood cell concentrated suspension for anemia was also discussed by MacQuaide and Mollison (1940).

*Hemoglobin-Ringer Solution:* While this is, strictly speaking, a crystalloid solution, it will be discussed at this point. The recent review of Fairley (1940) on the fate of extracorporeal circulating hemoglobin in man is of interest as well as the work of Amberson (1937) in this connection. The use of hemoglobin-Ringer's solution clinically in four patients with anemia was reported by O'Shaughnessy, Mansell, and Slome (1939). After preliminary alkalization of the urine, amounts of 600, 200, 250, and 1,000 c.c. of 5 per cent solution were given intravenously in an hour or less to the four patients respectively.

*Recent Publications:* Recent papers on blood transfusion are many, especially in the British medical press. Reviews include those of Du Bois and co-workers (1940), Douglass (1940), Ravitch (1940) on the technique of the blood bank in the Johns Hopkins Hospital, Wilson and Jamieson (1938), Bull and Drew (1940), and De Gown and Hardin (1940) on preserved blood. Hammond's recent (1940) remarks seem to be unique in casting doubt on the value of blood transfusion.

The use of sulfanilamide as a preservative of stored blood was studied by Novak (1939) and Hunwicke (1940). The latter reported that the concentration suggested by Novak (1:5,000) was not adequate and advised a 1:1,000 dilution. This higher dosage would mean 0.5 Gm. of sulfanilamide in each 500 c.c. blood transfusion. This dose is not large. The sulfanilamide must be dissolved in about 12 c.c. of warm water before mixing with the blood. Other techniques of preparing, storing, and administering preserved blood include those of Elliott, Macfarlane, and Vaughan (1939), and of Boland, Craig, and Jacobs (1939). Corelli (1940) advised a proprietary Italian thiosulfate preparation as a blood preservative, "Novotrans."

Diggs and Keith (1939) in two articles summarize their experiences during the first year of using a blood bank at the John Gaston Hospital in Memphis. In a series of 1,415 transfusions there was a reaction rate of 6.7 per cent and 5 deaths. They advise a test for hemolysis just before using all preserved blood samples. This is important because the detec-

tion of hemolysis by looking at the blood in a flask is unreliable, for it may appear to be hemolyzed when it is not, or the supernatant layer may be clear even when there is gross hemolysis in the cell layer. Edwards and Davie (1940) gave an account of the first 1,500 bottles of preserved blood distributed by the Merseyside War Blood Bank. Similar to the practice at the John Gaston Hospital, Memphis, they use the blood left in the taking tube in testing for Wassermann reaction, etc. Five per cent reactions (rigors) occurred following the giving of the blood. In a series of 951 transfusions, De Gowin and Hardin (1940) found 3.68 per cent reactions.

The "closed citrate method of collecting blood" used by Diggs (1940) at the blood bank of the John Gaston Hospital, Memphis, has several advantages in simplicity. Eliminating mechanical suction devices, the blood is allowed to run downhill into a single sterile bottle containing citrate. The blood left in the tubing at the completion of the procedure is collected and utilized for serologic tests and for typing and cross-matching.

Besides the danger of incorrect typing and cross-matching there is always the danger of intragroup reactions in the blood transfusion as pointed out by Wiener and Peters (1940) and others. Knoll and Schürch (1938) reported on the use of heparin in blood transfusion. Heparinization of the donor seemed to exert no ill effect on him or on the recipient.

Stead (1940) studied the collapse following sudden removal of large amounts of blood from professional donors kept in the horizontal position. After removal of 760 to 1,220 c.c., five of the six donors developed collapse when from 15.5 to 19.7 per cent of the total blood volume was removed. The collapse was accompanied by tachycardia and sweating of the forehead and coolness of the hands and feet. In the early stages there were no cerebral symptoms, the supply of blood to the brain being adequate. The onset of the collapse was sudden with a sharp blood pressure fall to 50 mm. Hg or below. At the height of the reaction there were bradycardia, nausea, and blurred vision.

The idea recently expressed in an article in the French literature by Bécart (1939) that all transfusions should be given rhythmically, i.e., by means of an artificial "heart" with intermittent pulsatile pressure, has not been widely adopted. Bécart believes that the manner of injecting is as important as the substance injected. Another type of transfusion is the continuous reciprocal method as used by Duncan, Tocantins, and Cuttle (1940).

Glinskiy (1940) found that warming did no good in blood transfusions. In using unwarmed (10 to 20° C.) blood there were 26.1 per cent reactions, while in a previous group of 1,400 transfusions of prewarmed blood there were 38 per cent reactions.

Cooksey (1940), in discussing the blood bank at Harper Hospital, Detroit, stated that all blood is converted into useful plasma when it is seven days old. Whole citrated blood is used, and following administration of the first 700 bottles of blood from the bank, only eight reactions occurred, most of them being very mild. This low incidence of reactions is in marked contrast to that of previous years with fresh blood.

The recent symposium on blood banks at the Detroit Regional Meeting of the American College of Surgeons, April 1, 1940, brought forth several interesting points. E. H. Schirmer reported on three years' experience with the Cook County Hospital blood bank. In 1936, before instituting the bank, there were 7 per cent reactions. Last year in a series of 6,446 transfusions there were only 1 per cent. She stated that they still use the sodium citrate-saline solution as they believe the De Gwin glucose solution favors hemolysis. The blood is given at the rate of 40 to 60 drops per minute. W. B. Cooksey stated that there was only one reaction in the last 407 bank blood transfusions at Harper Hospital, Detroit (0.25 per cent). Scudder emphasized four points to be remembered in using a blood bank: (1) chemical cleanliness, (2) rapid turnover of specimens, (3) slow administration, and (4) narrow plasma-cell interface in preserving flasks.

The disadvantages of stored blood would seem to rest in deterioration, largely from diffusion of electrolytes such as potassium and magnesium from the cells into the plasma. This is especially rapid when blood is transported and this again limits the use of stored blood. Scudder (1940) remarked in this regard: "In hemorrhage and shock, when the need for blood is the most urgent and where preserved blood might find its chief usefulness, its improper use would seem to carry the greatest danger." It would seem that most of these objections to stored blood could be obviated by using stored plasma.

*Cadaver Blood:* The use of cadaver blood in the treatment of shock was introduced by Dr. Skundina, a female assistant of Prof. Serge S. Youdine (Judin, Yudin),\* of the Institute Sklifassovsky (Central Emergency Hospital), Moscow. Youdine (1936) reported further on the use of cadaver blood. It was given a brief trial in actual practice at the Philadelphia General Hospital. Moore (1938) reviewed the use of cadaver blood in Chicago and an editorial in the *Journal of the American Medical Association* (1938) reviewed the entire subject.

In June, 1939, I spent two days with Professor Youdine and watched the entire setup and use of cadaver blood transfusions. The choice of cadavers is one of the most important items. Youdine manages all the emergency cases in Moscow, controls all the ambulances, and has three telephone operators working night and day answering emergency calls only. He thus has an enormous amount of material to choose from. A total of 1,054 cadavers were used in the three-year period 1935-1937.

\*Professor Youdine told the writer that he prefers this spelling, believing it to be a more accurate translation of the Russian alphabet.

A total of 1,738 liters of blood was obtained and of this 228 liters were discarded because of positive Wassermann reaction or other diseased condition. The average blood per cadaver was 1,650 c.c. and the average time after death that the blood was obtained was two and one-half hours. Some of the cadavers were traumatic cases:

	CADAVERS	USED
Fracture of skull	22	15
Gunshot wound of head and thorax	9	8
Closed thoracic trauma	16	10
Combined trauma	20	12
Buried in earth	7	6
Electrocution	34	29
Total	108	80
		74%

But by far the largest part of the blood was obtained from patients with angina pectoris. Youdine gets 10 to 15 male deaths from angina pectoris a day! Of the angina pectoris deaths 74 per cent are males and these make the best cadavers, rarely having a positive Wassermann. To show how many cadavers are discarded: in 1932 to 1934, of 5,104 cadavers transported by Youdine's ambulances, only 1,432 (28.5 per cent) were brought to the hospital for use, the others being taken directly to the morgue.

In obtaining the blood it is best to wait 1 to 3 hours after death but not more than 6 to 10 hours, the time being less in warm weather. The cadaver is placed on a table in Trendelenburg position, the neck sterilized with iodine, and the cadaver draped with sterile sheets. The operator wears sterile gloves and gown. With sterile instruments the external jugular vein is exposed and two glass tubes are inserted. These are 0.75 in diameter and 15 cm. long. A straight tube is placed toward the thorax and a right-angled tube toward the head. The blood is allowed to flow by gravity into sterile containers. It is then placed in a refrigerator and the process of fibrinolysis occurs spontaneously after clotting. It is this process that was Skundina's great discovery in 1930. Cadaver blood was first used on March 23, 1930.

In a series of 1,157 transfusions with cadaver blood there were 214 reactions (18 per cent) with 0.2 per cent deaths. All 3 deaths occurred in cases where a small transfusion of only 250 c.c. blood was used. The time of storage up to thirty-five days seemed to make little difference in the reaction rate. Youdine is such a firm believer in transfusion that he told the author: "The vein is for transfusion." The subject of blood transfusion will be discussed below under the heading "Shock in Wartime."

(To be concluded in the April issue. The references will accompany the last section.)

# Review of Recent Meetings

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## REVIEW OF THE FIRST MEETING OF THE SURGICAL INVESTIGATIVE SOCIETY OF THE SOUTH, OCT. 6 AND 7, 1940, VANDERBILT UNIVERSITY SCHOOL OF MEDICINE, NASHVILLE, TENN.

MICHAEL DeBAKEY, M.D., NEW ORLEANS, LA.

*(From the Department of Surgery, Tulane University School of Medicine)*

THE Surgical Investigative Society of the South has been organized from a group of southern surgeons. The purpose of the organization is to band together a small group of contemporaries, interested in surgical progress, and by annual meetings at some medical center to exchange ideas and to see for themselves the advances and research, in progress.

"The first meeting was held at Vanderbilt University in October. The first day was given over to procedure of organization and to a general discussion, initiated by the members themselves, as to researches being conducted by them and at their particular home locations.

"Officers elected were: Dr. Ira A. Ferguson, Atlanta, Ga., president; Dr. Michael E. DeBakey, New Orleans, La., vice-president, and Dr. Henry Poer, Atlanta, Ga., secretary-treasurer.

"The next meeting is to be held in Baltimore in October, 1941.

IRA A. FERGUSON, President."

Samuel McLanahan, Baltimore: *The Use of Sulfanilamide, Sulfapyridine, and Sulfathiazole on the Surgical Service of Johns Hopkins Hospital (abstract\*)*.—With the development of new derivatives in the sulfanilamide group, the indications for and use of these drugs are undergoing constant change. Sulfanilamide, however, continues to hold its place in the treatment of hemolytic streptococcal infections. In Welch bacilli infections it has proved effective clinically. Especially has it been used prophylactically in compound fractures and other open wounds. Introduced locally in the wound it has apparently been effective and has not interfered with wound healing.

Sulfapyridine was a welcome addition to the series, but in actual practice it is being replaced very largely by sulfathiazole. The latter drug is less likely to produce nausea but more likely to produce a rash and the troublesome drug fever.

In abdominal surgery, sulfathiazole is achieving special success. Recent reports by A. F. Jonas indicate its effectiveness in treating and preventing peritonitis. It has been given as a routine measure in the postoperative treatment of ruptured appendicitis and abdominal trauma, and as a preoperative measure in operations upon the colon. The sodium salt, not yet available commercially, has

\*Reports of papers so designated are abstracts prepared by the indicated authors themselves.

frequently been employed for intravenous use. Rectal strictures due to lymphopathia venereum have responded to sulfanilamide, sulfapyridine, and another drug, sulfanilic acid.

The future gives promise of the development of new compounds, one of which, sulfanilylguanidine, has already been reported by E. K. Marshall and his associates. This drug is poorly absorbed and so remains in high concentration in the intestinal tract. Its bactericidal effect upon diseases of the intestine and upon the intestinal contents is being carefully investigated. Doubtless much more will be heard of this drug in succeeding months.

**Discussion:** **Gaston Gay**, Atlanta, asked McLanahan what experience he has had with giving sulfathiazole per rectum. He reported three cases of peritonitis in which it was difficult to give the drug by mouth. One patient who received sulfathiazole had a rise in temperature and diarrhea following the use of the drug. **Ambrose H. Storck**, New Orleans, stated that he and his associates had anticipated and planned to use these drugs in gunshot wounds, but it so happens that the incidence of gunshot wounds had decreased. He expressed the opinion that the use of sulfanilamide in the form of hypodermoclysis, as suggested by Ravdin, has been of distinct benefit in their experience. **William H. Prioleau**, Charleston, S. C., agreed with McLanahan's statement about the use of sulfanilic acid in rectal strictures. In Charleston they have had quite a large series of these patients and they have been reviewed by **Edward Parker**, former resident surgeon in Vanderbilt Hospital. His findings are in absolute agreement, that the patients are more comfortable, the discharge is less, but the physical characteristics remain about the same. They have had about twenty of these patients of all kinds under observation. **Michael DeBakey**, New Orleans, directed attention to the use of these drugs in gas bacillus infections. He referred to some investigative work done in the Department of Experimental Surgery at Tulane University by **A. B. Longacre**. It was found that in *Clostridium welchii* infections in guinea pigs these drugs were of little, if any, value. Although their clinical experience was limited, it was their opinion that the drug has not been of definite value in these cases. However, he emphasized the fact that it was difficult to evaluate results of therapy in these infections, because of the numerous factors involved. **D. Henry Poer**, Atlanta, asked if some side results which might be dangerous had been observed in the use of sulfathiazole and sulfanilylguanidine. Because these drugs are being used so commonly, it would be worthwhile to direct attention to any untoward effects which they might produce. **Richard T. Shackelford**, Baltimore, mentioned one other type of case in which it was very useful; that is as a prophylactic in resection of the jaw. Resection of the jaw is in the mouth, a very dirty field. He has used sulfanilamide six times with large resections of the jaw. The wound in each case healed per primam. Sulfathiazole was used the last four times and in each case the wound healed per primam. **Clarence E. Gardner**, Durham, N. C., asked if there is any ill effect from the preoperative use of the drug from the standpoint of anesthesia or from the standpoint of wound healing in resection of the jaw. **George T. Wood**, High Point, N. C., stated that recent experiences with sulfathiazole tempted him to see how much protection could be obtained from the preoperative administration in acute inflammatory pelvic conditions. Two weeks ago a case was seen with acute pelvic peritonitis, with temperature of 103 to 104° F. The patient was extremely sick. After three days' administration of sulfathiazole, there was a drop in temperature, a diminution in vaginal discharge, and a diminution in the abdominal pain. Eight days after the administration of the sulfathiazole, the patient was operated upon. The postoperative reaction was much less severe than is usually present. **Ralph M.**

Larsen, Nashville, Tenn., stated that he and his associates have had a moderate amount of experience with sulfanilamide, extending for a period of eighteen months. They have treated sixty-eight cases of lymphopathia venereum. It has been very definitely shown in that group that there is almost complete disappearance of the inflammatory reaction. Colostomy was done in about 5 per cent. The average gain in weight of those treated with sulfanilamide has been somewhere in the neighborhood of 50 per cent. In general, the inflammatory reaction has failed to recur even after sulfanilamide has been discontinued for six to nine months, except in those instances where there is marked persistence of the stricture. The greatest benefit received from it was in early lymphopathia venereum. He did not know how many early acute cases there are in this study. Their experience has been that given an early case with proctitis as an initial lesion, with extensive edema and early ulcer, it can be healed with no stricture whatever if the patient is placed on sulfanilamide and if necessary given a temporary colostomy. He had recently seen a case which brings up the question as to whether or not in the presence of pneumococcus infection or compound fracture one would give sulfathiazole in the light of the evidence at the present time that sulfathiazole is not readily excreted by the choroid plexus.

Regarding Gay's question about the rectal administration of the drug, McLanahan, in closing, admitted that he and his co-workers have had no personal experience nor do they know of any experience in the rectal administration of sulfathiazole. The fact is the intravenous drug just happens to be available. The rectal administration would be certainly very important to follow. They have not seen diarrhea accompanying the drug, but a patient occasionally may get it. As regards Welch bacillus infection, it was his understanding that Welch bacilli many times are mixed up with streptococcus, and some of the effect of treatment may be because streptococci may be present in the infection in the laboratory animal. From clinical experience with a number of cases it was his opinion that many times amputations have been avoided. However, there are many things one can do for such patients and he thought all should be done as far as possible. In regard to side reactions, as mentioned by Poer, complications can be listed in eight different groups. In addition to the two mentioned, drug fever and rash, there are blood changes which are familiar and which should be looked for. It demands careful observation of the blood picture. There may be jaundice. There may be psychosis, which he had observed in a child receiving sulfathiazole. The child was completely disorientated and confused. These are among the important side effects. As regards Wood's remarks about pelvic irritations, their resident had observed a series of appendiceal cases in which these drugs were used. It was found that the wound heals much more promptly, there is less discharge, and there is a cleaner looking wound and fewer secondary abscesses. The resident reported that he and the other surgeons use fewer drains in ruptured appendix, possibly one cigarette drain instead of three, and that the healing is more prompt and the hospital stay shorter. As regards Larsen's remark about the treatment of early lymphopathia venereum, it would certainly be important if it is possible to keep those cases from going on to permanent stricture formation. In regard to head injuries, there are a number of factors to be considered. McLanahan stated that at Johns Hopkins Hospital, W. E. Dandy is experimenting on the application of these drugs in postoperative infections and compound head injuries. He does not think it is effective in brain abscesses, because they are well walled off from the blood supply.

Richard T. Shackelford, Baltimore: *Peritoneoscopy* (abstract).—Peritoneoscopy has been used in Baltimore as a diagnostic procedure since February, 1935.

The examination has been performed in eighty cases and from this experience we believe it is especially indicated to establish the diagnosis in suspected cirrhosis of the liver, metastases to the liver or peritoneum, inoperable carcinoma of the stomach, tuberculous peritonitis, carcinoma and cysts of the ovary, ectopic pregnancy, myomata uteri, and pelvic inflammatory diseases.

We believe that it should not be used in acute abdominal inflammatory disease, abdominal distention, or where many adhesions are known to be present. Furthermore, it should be resorted to only if the usual simpler laboratory procedures have failed to determine the diagnosis.

The limitations of the method must be kept in mind and it should be used only for a specific purpose, as to (1) establish a differential diagnosis, (2) confirm a previous diagnosis, (3) determine the nature, location, and extent of a tumor.

In our series the intestine was perforated in one case, but without any serious effect. There were no other complications. The procedure resulted in an incorrect diagnosis in one instance and was unsuccessful due to adhesions in three others. There were no fatalities.

We believe it is a valuable diagnostic procedure in a small number of selected cases, and in such a group will prevent many unnecessary exploratory laparotomies.

**Discussion:** Rawley M. Penick, Jr., New Orleans, stated that, although he has had no experience with this procedure, he has not been able to get enthusiastic about it for several reasons. One is that it does have dangers. Another is that it seems to him that one is dealing with conditions that are finally operative. He asked Shackelford if he knew how many of these patients subsequently did have laparotomies. He also made the point that an exploratory laparotomy can be done very easily under local anesthesia. He wondered if more information could not be obtained in this way than with this instrument. He had gotten the impression that it necessitates operation later anyway, so its value is somewhat nullified for that reason. The greatest information is to be found in the liver. Michael DeBakey, New Orleans, agreed in general with Penick. Although he has had no personal experience with it, one man in their department had performed the procedure in thirty or forty cases. In this group of cases the procedure had not proved of distinct informative value and in some the findings were definitely misleading. He asked if false information had been given in Shackelford's series. Obviously, usage and experience are important factors. However, it was the general impression that the indications were definitely restricted. Ambrose H. Storek, New Orleans, stated that as regards penetrating wounds of the abdomen, Griswold and his associates in Louisville, Ky., have had quite a number of cases of penetrating wounds of the abdomen in which they felt that the use of the peritoneoscope had helped them to recognize a few cases with actual perforation and hemorrhage which otherwise they might have missed. He believed that in acute abdominal conditions it might find a place. In borderline cases, especially in instances of other injuries where abdominal exploration is to be avoided if possible, he was of the opinion that it may be valuable.

William H. Prioleau, Charleston, S. C., agreed with Shackelford that there is a very definite place for it. In fact, they have saved a great many hospital days and saved a certain number of laparotomies. It has been mainly used in a small series for diagnosis of carcinoma, particularly of the ovary, which had not been diagnosed otherwise and in which the patients were not subjected to hospitalization.

Shackelford, in closing, stated that, in answer to DeBakey's question, false information was given in his thirteenth case, curiously enough, and so from that time on it has been his custom not to give information in which there is any reasonable doubt, in which there is actually any doubt. By means of biopsy it is possible to determine with accuracy what is present. If he is not sure of it, it is recorded as undeterminable by peritoneoscopy. That has occurred in three cases which were noted as "unable to determine diagnosis." The instrument should not be used just for general inspection of the abdomen. It should be used to answer only specific questions: Is this carcinoma of the liver or cirrhosis of the liver? Is it metastasis to the liver? Is the spleen enlarged or is it small? If it is enlarged, a biopsy should be made to see what the microscopic picture shows. In other words, it should be used for making differential diagnosis, not just for a general inspection of the abdomen. A diagnosis should not be made unless one is certain. In regard to Penick's question, he did not have these particular figures on the entire 80 cases, but he had the figures on the first 50 cases. In the series of 50 cases they saved 22 exploratory laparotomies. In regard to Storek's remark, he stated that he was familiar with Griswold's work. Their procedure in penetrating wounds of the abdomen is to insert the peritoneoscope and see if perforation of the peritoneum, and not of the intestine, has occurred. He would not trust any opinion one could give as to whether the intestine was perforated by a bullet or a stab wound. One could see, of course, whether there is a hole in the surface of the peritoneum. They have reported 6 cases. There have been 28 instances reported by various authors in which they used peritoneoscopy to determine the presence or absence of hemoperitoneum.

John V. Goode, Dallas, Tex.: *Experiences With a Transverse Abdominal Incision* (abstract).—The disadvantages of the transverse abdominal incision in the upper abdomen are: (1) This incision is not suitable for exploratory procedures. (2) Occasionally the transverse incision is not adequate and the operation must add a midline incision to the transverse incision. (3) The transverse incision takes a few minutes more time than does a vertical incision. (4) The upper portion of the wound is in the way when the operation is one to explore the common duct. (5) If a hernia develops, its repair may be more difficult if it is close to the costal margin.

While these disadvantages are real, they are outweighed by the very real advantages of the transverse incision. The advantages are: (1) The closure is more secure than the closure of the vertical incision because the transversalis abdominis muscle is divided parallel with its fibers and consequently every cough or breath does not tend to pull the wound apart. (2) This incision is more efficient in that all of it is used and not just the upper angle. (3) The transverse colon and omentum keep the small bowel out of the wound. This tends to prevent shock and to prevent adhesions. (4) The exposure is ideal. (5) There is no injury to nerves and consequently no atrophie or weak muscle following this incision. (6) Disruption and hernia seem to be less frequent following the use of the transverse incision. (7) Of great importance is the lessening of pain following this incision. With the freedom from pain there will be deeper respiratory movements, less atelectasis, and less pneumonia.

Discussion: Michael DeBakey, New Orleans, directed attention to the lower transverse incision, particularly for appendectomy. In Tulane University surgical service, the transverse incision has been used for a number of years. It has practically all the advantages enumerated for the upper transverse incision. It has the advantage over the McBurney incision that better exposure may be ob-

tained, pelvic exploration can be done, and the incision may be more easily enlarged. This incision is frequently referred to as the Davis incision, but Elliot described it in 1896 (Boston M. & S. J. 135: 433) and Rockey in 1905 (Med. Rec. 68: 779). It is performed by making the incision horizontally on a level with the anterior superior iliac spine, extending from a few centimeters medial to this point to a few centimeters lateral to the midline. The external oblique aponeurosis and the lateral half of the rectus sheath are incised in line with the skin incision, exposing the rectus and internal oblique muscles. The former is retracted medially and the fibers of the latter as well as those of the transversus abdominis are separated. The peritoneal cavity is entered by extending the incision transversely through the lateral half of the rectus sheath and the transversalis fascia. Paul W. Sanger, Charlotte, N. C., asked about the wisdom of using silver wire. James A. Kirtley, Jr., Nashville, asked Goode if he uses this incision in many early cases of perforated ulcer.

Goode, in closing, stated that, as far as silver wire is concerned, he adhered to his training in Cincinnati. When he uses silver wire, nothing else is used. In the case of early ulcers he uses only silver wire.

Clarence E. Gardner, Jr., Durham, N. C.: *Certain Observations of the Use of the Digital Oscillometer in the Recognition of Peripheral Vascular Diseases* (abstract).—An instrument was presented which measured the magnitude of pulsations of the arteries of the fingers and toes. It had been made in the instrument shop at Duke University. Charts showing the range of pulsations in the digits of normal individuals at various temperatures were presented. Charts showing the range of pulsations in the digits of patients with Raynaud's disease and also with obliterative vascular diseases were also presented. The ability of the instrument to record changes in pulsations before and after smoking and before and after sympathectomy was demonstrated. It is thought that the instrument will be of value in differentiating vasospasm from obliterative vascular diseases.

Discussion: John V. Goode, Dallas, asked Gardner about the width of the cuff, because this is considered significant. As to the degree of oscillation, he also asked if the amount of mercury used to bring it up would have any significance whatever in the blood pressure of the finger. Samuel McLanahan, Baltimore, stated that he observed variations of waves in all cases. He asked if one always gets oscillations even though palpable pulsations may be absent. Michael DeBakey, New Orleans, emphasized the significance of vasospasm in peripheral vascular disease. Its importance lies in the fact that it forms the one controllable factor from the standpoint of therapy. For this reason it is important to determine not only the presence or absence of vasospasm, but also its extent. For practical purposes an apparatus of simpler construction than that described by Gardner would be desirable. The instrument used in the peripheral vascular clinic at Tulane University has been one similar in principle to one constructed by Roy Turner, of the Department of Medicine at Tulane University. This apparatus is a recording oscillometer, but in its simpler form may be applied clinically without the recording unit, which is the complicated part. D. Henry Poor, Atlanta, stated that it seems to him in studying peripheral vascular conditions that in the past we have had certain diagnoses handed to us, such as thromboangiitis obliterans, Buerger's disease, and arteriosclerosis with spasm or perhaps without spasm. On the other hand, a large number of patients are encountered who do not fall into one of these groups, and it seems that this occurs to such an extent that it is difficult to classify them. The instrument described may be of some value in such cases. Another important problem in the treatment of

peripheral vascular disease is the element of smoking, whether it be in the 10-year-old boy he has mentioned or the 60-year-old man. It seems that this is a habit which is very difficult to break and one practical value in an apparatus of this sort is that you can take a man into a constant temperature room and show him the figures so that he can see the temperature changes in his digits or in his toes and also how his oscillations vary in his blood vessels. It might be a very good way to sell a patient on the idea of stopping something that is distinctly harmful.

Gardner, in closing, emphasized Poer's remarks about smoking. They have used this instrument in obliterative disease, arteriosclerosis, and Buerger's disease. In all of them it was found they had no pulsations at all in the digits. As regards McLanahan's remarks, one frequently finds normal pulsations at the wrist and ankle and normal oscillogram curves, but still the patient has disease of the peripheral vessels. It is in such cases that this instrument is helpful. As regards the instrument mentioned by DeBakey, he was of the opinion that it was not of great clinical value. The plethysmograph perfected by Johnson in Chicago is an excellent apparatus. It is very exact and does the same thing as this instrument he has designed. Their difficulty has been in getting the thing to work. The plethysmograph takes a trained technician to make it work and they were not skillful enough or did not have the patience when something was wrong, and so gave it up. It is on the market and is successfully used at this time. The great value of the one he presented is that the whole extremity can be immersed in a water bath. Those working with this know that there are great variations in pulsations. They are not equipped with a constant temperature or constant humidity room and find it easier to immerse the extremities. Goode asked about the width of the cuff, but he stated that he was not enough of a physicist to answer that.

Paul W. Sanger, Charlotte, N. C.: **Demonstration of the Tourniquet Technique for Lobectomy in Bronchiectasis** (movie in color) (abstract).—My purpose in showing this movie was not to demonstrate anything new or unusual, but merely to emphasize the fact that we, as general surgeons, have relegated the specialty of thoracic surgery to so-called specialists in this field, which was developed originally by general surgeons, because, after all, only the well-founded principles of general surgery are applicable, and I think we are grossly negligent not to emphasize and discuss thoracic problems more often than we do. I am presenting here the technique that I used in 8 cases with bronchiectasis which was limited to one lobe or more, 5 of which had bilateral lower lobe infection. In 2 patients the pathology was limited to the lower lobe (unilateral). One was a patient with all three lobes involved on the right.

I prefer the tourniquet method because: (1) it is simpler than the individual ligation of vessels and bronchus; (2) it is dangerous to attempt individual ligation in the presence of edematous inflammatory tissue; (3) it is not necessary to resect the involved lobe or flush with the hilum; (4) on account of the likelihood of a bronchial fistula developing, it is quite natural that a smaller bronchus would occlude much quicker than a larger and more rigid tube.

I might re-emphasize pertinent points of this technique. As you will note, the incision is a postlateral one, paralleling the seventh intercostal space and extending to the anterior axillary line. Segments of the seventh and eighth ribs are removed posteriorly, thus allowing the maximum spreading of the ribs. After the involved lobe is freed of its adherent attachments and the pulmonary ligament is severed, a tourniquet is applied to the hilum. A pleural cuff is developed and thence the lung is excised by gradually cutting in a circular manner within a few centimeters of the tourniquet. The stump is occluded with interrupted

chromic catgut, after which the raw surface of the stump is covered with the previously prepared pleural cuff. Two catheters are inserted inferior to the incision. The anterior one is used to withdraw the encased air and is removed in from eighteen to twenty-four hours. The posterior catheter remains in place indefinitely. Closure is carried out by reapproximating the ribs with interrupted black silk. The muscles are closed in layers with catgut and the skin with silk. It is also noted that these patients are all transfused during operation.

I would like to mention one other patient who had bronchiectasis associated with squamous carcinoma of the bronchus. In this case individual ligation technique was followed.

These patients range in age from 6 to 55 years. Five were males and 4 were females. The cause of pathology in 4 of these cases was due to aspiration of foreign bodies, 2 represented questionable congenital cystic diseases of the lung, 2 developed falling measles and whooping cough, and 1 was the malignancy which was mentioned above.

Of these patients there are 5 complete cures, but the other 4 had bilateral involvement prior to operation and are now being followed for the possibility of doing further surgery.

**Discussion:** Michael DeBakey, New Orleans, stated that he and his co-workers previously employed the technique of tourniquet ligation as described by the essayist, but more recently have used individual ligation of the hilar structures. It was found that the incidence of pleural infections was diminished and the postoperative stay in the hospital considerably decreased. J. A. Kirtley, Jr., Nashville, asked Sanger if he left the tourniquet on. I. A. Ferguson, Atlanta, asked if Sanger ever crushes the phrenic nerve.

Sanger, in closing, stated that the point DeBakey made about hospitalization is well brought out. The last patient he had was discharged in three weeks. They have found that patients may leave the hospital unusually early. If they have inflammatory tissue, it is rather hazardous to try individual ligation. At the same time, he believed that, if bronchial infection is present, it should be done. He thought the other method is simpler. He never leaves the tourniquet on.

**Michael DeBakey, New Orleans (Leader): Round-Table Discussions on Suture Material and Wound Healing (abstract):** DeBakey prefaced the discussion by stating that the purpose of the round table was to present an opportunity for the members to discuss informally some surgical subject previously selected of current interest. Such a discussion would permit members of various sections to express their opinions and experiences and help crystallize a more rational comprehension and perhaps allow a better evaluation of the subject.

Because of the recent revival of interest in suture material, it was selected for this discussion. In the surgical service at Tulane University they had previously employed catgut and this was followed by the use of silk. On the basis of extensive experimental studies done in the Experimental Laboratory at Tulane by Alton Ochsner and Wm. Meade, it was found that cotton was the most desirable suture material. This was verified clinically and at present cotton is used exclusively. The advantages of cotton are that it produces minimal tissue irritation, is pliable and easily sterilized, is of sufficient strength in appropriate sizes, and is economical. Its tensile strength in tissue decreases considerably less than catgut, silk, or linen.

In clinical practice it should be realized that Halsted's rules regarding the use of silk must be strictly adhered to in the use of cotton. Ordinary spool cotton thread as bought in a notion store is employed. It is prepared by wrapping it on

rubber tubes and autoclaving it for fifteen minutes at 15-pound pressure or by boiling for twenty minutes. For ligation of small vessels in the subcutaneous tissue or other areas, No. 60 or 80 is used. For approximation of the peritoneum or fascia, "quilting cotton" is employed. A heavier material is rarely necessary, but occasionally No. 10 mercerized crochet cotton may be required. Samuel McLanahan, Baltimore, asked about cotton in the face of infection. DeBakey stated that on the basis of their experience one of the most important uses of nonabsorbable suture material is in contaminated wounds. Cases in which cotton was used in severely infected wounds have been observed to heal without sinus formation or the extrusion of the sutures. Apparently this complication is less likely to occur with cotton than with silk. Moreover, the use of a nonabsorbable suture material in the presence of infection is considered more desirable than the use of absorbable material because wound disruption is believed to be more likely with the latter for two reasons; first, the infection delays wound healing; and second, the liberated proteolytic ferments cause early digestion of the suture material. John V. Goode, Dallas, stated that he has used cotton ever since an article appeared in the *Journal of the American Medical Association*, in which a case was described of a colored woman who had the external carotid tied and no cotton came out in spite of wound infection. An important advantage is that it can be so easily sterilized. He stated that in a case in which the ovaries were removed the skin edges were closed with a subcuticular piece of cotton. It has now been six months and a little piece of cotton is still there and there has been no reaction. He has watched this with a great deal of interest. Donald Donaldson, Birmingham, Ala., asked if silk is used to close the peritoneum and if continuous sutures are ever used. DeBakey answered that cotton is used all the way through and that interrupted sutures are used exclusively. He emphasized the importance of cutting the suture down on the knot. To facilitate this a special suture scissors has been devised and was described in the *J.A.M.A.* 112: 2410, 1939. Richard T. Shackelford, Baltimore, stated that one other suture material has been overlooked and that is alcohol-preserved fascia. Not many surgeons use it. Their experience has been that there is considerable accumulation of fluid interfering with the healing of the wound. Probably fascia is not used in the proper way. He and his associates have used it a great deal. This includes about 185 to 190 hernia patients. Experience has shown that, if the fascia is properly soaked before the time of operation, accumulation of secretion does not occur. If an operation is to be done at 9:00 A.M., the nurses place the alcohol-preserved fascia in a basin of salt solution as soon as they enter the operating room at 7:30, one and one-half hours before time to start the operation. Then it is changed to a fresh basin of solution and left there until 9:30 or 9:45. Frequently in large postoperative hernia one saves a great deal of time by not having to make a long incision in the thigh to obtain aut fascia. There are many times when one cannot dissect a section of the rectus sheath. Alcohol-preserved fascia can solve a lot of these difficulties, and the secret of its proper use is the elimination of the chemical element. They have used it on animals and in human beings and have seen little, if any, difference in any way in the healing with alcohol-preserved fascia and aut fascia.

Alfred Blalock, Nashville: *Activities of National Research Council in Preparedness* (abstract).—At the request of the Surgeon-General of the Army and Navy, the Division of Medical Sciences of the National Research Council has appointed certain committees which are acting in an advisory capacity. The talk consisted of a brief description of the activities of the Committees on Shock and on Surgery.

**James R. Dawson, Jr., Nashville:** **Some General Aspects of Antirabic Immunization of Dogs (abstract).**—Rabies in dogs can be controlled most satisfactorily by prophylactic immunization. Vaccines available at the present time are extremely variable in their effectiveness. The ideal vaccine, theoretically, would be one which would immunize as a result of a mild nonfatal attack of rabies. Experiments are reported in which rabies virus, propagated in the brains of chick embryos, was used to vaccinate rabbits successfully against large test doses of street and of fixed rabies virus.

**Ann Minot and Katharine Dodd, Nashville:** **Fluid Equilibrium (abstract).**—The blood volume may be seriously reduced (1) by excessive loss of fluid and (2) by an inability to attract and hold sufficient water in the blood stream because of a primary lack of plasma protein or because of a progressive loss of protein through injured capillaries. In simple dehydration fluid equilibrium can be restored by replacement of solutions of the appropriate electrolytes. When there is a deficiency of protein in the blood stream, protein as well as fluid must be restored before a normal distribution of body fluid can be maintained.

**George S. Johnson, Nashville:** **The Treatment of Carcinoma of the Jaw (abstract).**—A series of cases of carcinoma of the jaw were reported in which operation had been carried out. Approximately one-half of this series were alive and well between two and five years after operation.

**Barney Brooks, Nashville:** **Effects of Pressure and Temperature on Ischemic Necrosis (abstract).**—It is generally known that varying degrees of stress and strain exist in normal tissues and that unusual amounts of intermittent or constant pressure applied to tissues produce pathologic changes. The effects of different amounts of pressure applied for different lengths of time upon the various tissues of the living animal are not definitely known. The tail of the rat is particularly well adapted for the experimental study of this problem, because the animal may be easily restrained and the tail contains so large a number of different structures readily subjected to known pressures for measured lengths of time.

In a series of experiments it was found that the amount of pressure and the length of time necessary for producing massive necrosis were remarkably constant in healthy animals kept at ordinary room temperature.

The pathologic changes produced by amounts of pressure or periods of time short of that necessary for massive necrosis were also studied. Epithelial hyperplasia, fibrosing myositis, and nerve degeneration were observed.

Modification of the temperature of the tissues during periods subjected to pressure was found to be a powerful determinant of the length of time necessary for pressure to produce massive necrosis.

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### COMPARATIVE RESULTS IN THE USE OF LIVING AND PRESERVED FASCIA AS SUTURE MATERIAL IN BONE

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LIVING fascia grafts have been much used in recent years as suture material in the repair of fractures and dislocations. Interesting papers on this subject have been written by Gallie and LeMesurier,<sup>1</sup> Patterson,<sup>2</sup> and Allen.<sup>3</sup> So far as we know, preserved fascia strips have been little used as suture material in fractures, and the only report of such use that we have at hand is that of Patterson,<sup>2</sup> who in one case used preserved human fascia lata to suture a fractured clavicle through drill holes in the fragments. The fascia strip used in this case had been left over from a hernia operation ten days before and preserved in Scott's acetone-alcohol-aqueous solution of mercurochrome in the meantime. The result obtained was just as good as the results obtained in other cases in which living fascia strips had been used.

Experimental work, showing the fate of living fascia transplanted into bone, has been done by Kernwein, Fahey, and Garrison.<sup>4</sup> They have shown that ossification of such transplants occurs.

The fate of preserved fascia grafts when transplanted into soft parts to repair defects was shown by experiments published by Koontz in 1926<sup>5</sup> and in subsequent years, but we know of no experimental work that has been done showing the fate of preserved fascia when transplanted into bone. We have, therefore, performed twenty-eight experiments on dogs, in which both living and preserved fascia were transplanted into bone in different ways, in order to show the fate of both types of fascia and to note any differences that might occur in the fate of the two types. In a few instances the fascia strips (both types) were

transplanted in such a manner that they had no function to perform, but in most instances they were given the function of holding separated bony fragments together.

*Experimental.*—The following is a record of some of the experiments. Experiments representing all the types of reactions obtained are given below. It is thought unnecessary to record each experiment in detail as this would entail a great deal of repetition. Dogs were used in all the experiments, and, whenever alcohol-preserved fascia was implanted, it was implanted on the right side of the animal, and likewise, living fascia was always implanted on the left side of the animal. This was done to avoid confusion in interpreting results.

EXPERIMENT K1 (Oct. 17, 1935).—*Fascia in Pubic Bone*: Midline incision over symphysis pubis. The ramus of the pubic bone was exposed on the left side, just lateral to insertion of left rectus muscle. About one-third of the thickness of the bone was chiseled away, exposing the medullary cavity. A strip of rectus sheath was excised and sutured around the bone, the flat side of the strip lying in the chiseled notch. The muscle and subcutaneous tissue were then sutured over the site of the operation. The ramus of the pubic bone on the right side was then exposed, and an alcohol-preserved strip of dog fascia lata was sutured in a similarly chiseled notch on this side. The wound was closed.

On Nov. 30, 1935 (44 days after operation), the dog was killed. The site of the fascial implantation was located on each side by the notch in the bone and by the silk sutures with which the strip was sutured in place. There was no callus formation. Very little fascia was seen in the notch on the left side, but a thin strip was visible on the right side.

EXPERIMENT K2 (Nov. 7, 1935).—*Fascia in Femur*: Left rectus incision. A piece of aponeurosis of the external oblique muscle was removed and split in two strips, one of which was placed in 70 per cent alcohol and the other in salt solution. Incision was then made over the left femur, with a mesial approach. The femur was exposed, and a hole was bored through it. The strip of fascia, which had been placed in salt solution, was then placed through the drill hole and tied around the lateral surface of the femur. The knot was transfixed and sutured with black silk. The wound was closed.

A similar operation was done on the right side, using the strip of fascia that had been dropped into 70 per cent alcohol at the beginning of the operation about three-quarters of an hour before.

On Nov. 29, 1935 (22 days after operation), the dog died. Autopsy showed a little evidence of the fascia remaining on each side. The holes in the bones were located on both sides, and the silk sutures showed the sites of implantation. There was no callus formation.

EXPERIMENT K3 (Nov. 14, 1935).—*Fascia in Scapula*: Midline abdominal incision, and a large piece of rectus sheath removed. Half of fascia was placed in salt solution and half in 70 per cent alcohol. The wound was closed.

The dog was then turned over, and the left scapular region was prepared for operation. Incision was made over left scapula. The muscle was separated, and the posterior end of the scapula was split with a saw in a longitudinal direction for about 1.5 inches. Holes were bored on each side of the slit, and a strip of rectus sheath from that which had been placed in salt solution was threaded through the holes and tied so as to steady the slit. The knot was transfixed with silk. The wound was closed.

On Nov. 21, 1935, the right scapula was operated upon in exactly similar fashion to the operation done on the left scapula on Nov. 14, except that a strip of alcohol-preserved rectus sheath, removed from the dog at the first operation, was used instead of living fascia.

On Jan. 9, 1936 (49 days after the first operation and forty-two days after the second operation), both scapular regions were explored. A firm ridge of healing could be felt in the bone on each side. The fascia on each side was identified by the transixed silk suture. The fascia had partially disappeared, but more was left on the right side than on the left.

EXPERIMENT K5 (Dec. 14, 1935).—*Rib Fusion Operation*: An incision was made over the right ribs, at about the junction of the upper and middle thirds of the chest. Two ribs were exposed. The periosteum was cleaned off, and the muscles were removed from between them. The cortex was then removed from the adjacent edges of the two ribs, and the ribs were brought together by tying around them, in two places, strips of dog fascia removed a week previously and preserved in 70 per cent alcohol. The more anterior strip was tied around the rib twice. The wound was closed.

On Jan. 25, 1936 (42 days after operation), the site of operation was explored, and the two ribs were found to be firmly fused by bony union.

EXPERIMENT K6 (Dec. 24, 1935).—*Rib Fusion Operation*: Two strips of fascia lata were removed from the left thigh, and the wound was closed. An operation exactly similar to that done in the previous experiment was then performed upon this dog, except that living fascia removed from the thigh was used instead of preserved fascia.

On Jan. 30, 1936 (40 days after operation), the site of the operation was explored, but no bony union was found between the ribs that had been tied together with the fascia strips. It was felt that this was due to the fact that the knots had possibly slipped somewhat and the ribs had not been held in close enough apposition.

EXPERIMENT K11 (Oct. 15, 1936).—*Suture of Olecranon With Living Fascia*: Incision was made over the left elbow. The olecranon was sawed in two. Holes were drilled through both fragments, and the fragments were sutured together with a strip of autogenous fascia lata removed from the left thigh. The wound was closed, and a plaster cast was applied.

On Jan. 27, 1937 (104 days after operation), a specimen was removed. There was evidence of firm union. X-ray showed bony union (Fig. 4). Microscopic section showed the fibers of the implanted fascia to be intact in the drill holes, but there was no ossification of the fascia (Fig. 7), although there was some encroachment on it by new bone at the sides of the drill holes.

EXPERIMENT K12 (Oct. 31, 1936).—*Suture of Olecranon With Preserved Fascia*: The right olecranon was exposed and sawed in two. It was then sutured with alcohol-preserved ox fascia lata, using the same technique as in the previous experiment. The wound was closed, and the cast was applied.

On Nov. 20, 1936, the cast had come off.

The dog was examined on March 20, 1937. Fragments were nicely approximated, but there was possibly very slight motion.

On May 25, 1937, there was slight motion and obviously only fibrous union.

On May 26, 1937 (7 months after operation), a specimen was removed. X-ray showed no bony union (Fig. 2). Microscopic section showed the fascia fibers to be intact, but there was no ossification of the fascia.

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On Nov. 29, 1935 (22 days after operation), the dog died. Autopsy showed a little evidence of the fascia remaining on each side. The holes in the bones were located on both sides, and the silk sutures showed the sites of implantation. There was no callus formation.

EXPERIMENT K3 (Nov. 14, 1935).—*Fascia in Scapula*: Midline abdominal incision, and a large piece of rectus sheath removed. Half of fascia was placed in salt solution and half in 70 per cent alcohol. The wound was closed.

The dog was then turned over, and the left scapular region was prepared for operation. Incision was made over left scapula. The muscle was separated, and the posterior end of the scapula was split with a saw in a longitudinal direction for about 1.5 inches. Holes were bored on each side of the slit, and a strip of rectus sheath from that which had been placed in salt solution was threaded through the holes and tied so as to steady the slit. The knot was transfixed with silk. The wound was closed.

On Nov. 21, 1935, the right scapula was operated upon in exactly similar fashion to the operation done on the left scapula on Nov. 14, except that a strip of alcohol-preserved rectus sheath, removed from the dog at the first operation, was used instead of living fascia.

On Jan. 9, 1936 (49 days after the first operation and forty-two days after the second operation), both scapular regions were explored. A firm ridge of healing could be felt in the bone on each side. The fascia on each side was identified by the transfixed silk suture. The fascia had partially disappeared, but more was left on the right side than on the left.

EXPERIMENT K5 (Dec. 14, 1935).—*Rib Fusion Operation*: An incision was made over the right ribs, at about the junction of the upper and middle thirds of the chest. Two ribs were exposed. The periosteum was cleaned off, and the muscles were removed from between them. The cortex was then removed from the adjacent edges of the two ribs, and the ribs were brought together by tying around them, in two places, strips of dog fascia removed a week previously and preserved in 70 per cent alcohol. The more anterior strip was tied around the rib twice. The wound was closed.

On Jan. 25, 1936 (42 days after operation), the site of operation was explored, and the two ribs were found to be firmly fused by bony union.

EXPERIMENT K6 (Dec. 21, 1935).—*Rib Fusion Operation*: Two strips of fascia lata were removed from the left thigh, and the wound was closed. An operation exactly similar to that done in the previous experiment was then performed upon this dog, except that living fascia removed from the thigh was used instead of preserved fascia.

On Jan. 30, 1936 (40 days after operation), the site of the operation was explored, but no bony union was found between the ribs that had been tied together with the fascia strips. It was felt that this was due to the fact that the knots had possibly slipped somewhat and the ribs had not been held in close enough apposition.

EXPERIMENT K11 (Oct. 15, 1936).—*Suture of Olecranon With Living Fascia*: Incision was made over the left elbow. The olecranon was sawed in two. Holes were drilled through both fragments, and the fragments were sutured together with a strip of autogenous fascia lata removed from the left thigh. The wound was closed, and a plaster cast was applied.

On Jan. 27, 1937 (104 days after operation), a specimen was removed. There was evidence of firm union. X-ray showed bony union (Fig. 1). Microscopic section showed the fibers of the implanted fascia to be intact in the drill holes, but there was no ossification of the fascia (Fig. 7), although there was some encroachment on it by new bone at the sides of the drill holes.

EXPERIMENT K12 (Oct. 31, 1936).—*Suture of Olecranon With Preserved Fascia*: The right olecranon was exposed and sawed in two. It was then sutured with alcohol-preserved ox fascia lata, using the same technique as in the previous experiment. The wound was closed, and the cast was applied.

On Nov. 20, 1936, the cast had come off.

The dog was examined on March 20, 1937. Fragments were nicely approximated, but there was possibly very slight motion.

On May 25, 1937, there was slight motion and obviously only fibrous union.

On May 26, 1937 (7 months after operation), a specimen was removed. X-ray showed no bony union (Fig. 2). Microscopic section showed the fascia fibers to be intact, but there was no ossification of the fascia.



1



2



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4



5



6

Figs. 1-6.—See opposite page for legend.

EXPERIMENT K13 (Nov. 10, 1936).—*Living Fascia in Olecranon*: Left olecranon was exposed, sawed in two, and sutured as above, using a strip of autogenous fascia lata removed from the left thigh. The wound was closed, and a plaster cast was applied.

On March 20, 1937 (4½ months after operation), a specimen was removed. Union appeared to be firm. X-ray showed fair apposition and some callus, but apparently no bony union from an x-ray standpoint, although clinically there was good bony union (Fig. 3). Microscopic sections showed osteoid tissue between the fragments, and, where the fascia traversed the bone, it had been largely replaced by bone (Fig. 8).

EXPERIMENT K14 (Nov. 12, 1936).—*Preserved Fascia in Olecranon*: The right olecranon was exposed, sawed in two, and then sutured by the technique described above, with a strip of alcohol-preserved fascia lata of dog. The wound was closed, and a cast was applied.

On Dec. 9, 1936 (twenty-seven days after operation), the dog died. Autopsy showed union of the fragments, but there was possibly very slight motion, suggesting that union was not quite complete. X-ray showed partial bony union (Fig. 4). Microscopic sections showed osteoid tissue between the fragments, and the drill holes in the bone contained fascia running into the space between the fragments and containing osteoid cells (Fig. 9).

EXPERIMENT K15 (Dec. 3, 1936).—*Living Fascia in Olecranon*: The left olecranon was exposed, sawed in two, and sutured in the usual manner with a strip of fascia from the left thigh of the same dog. The wound was closed, and a cast was applied.

April 17, 1937.—*Preserved Fascia in Olecranon*: The right olecranon was exposed, sawed in two, and sutured in the usual manner with a strip of alcohol-preserved dog fascia lata. The wound was closed, and a cast was applied.

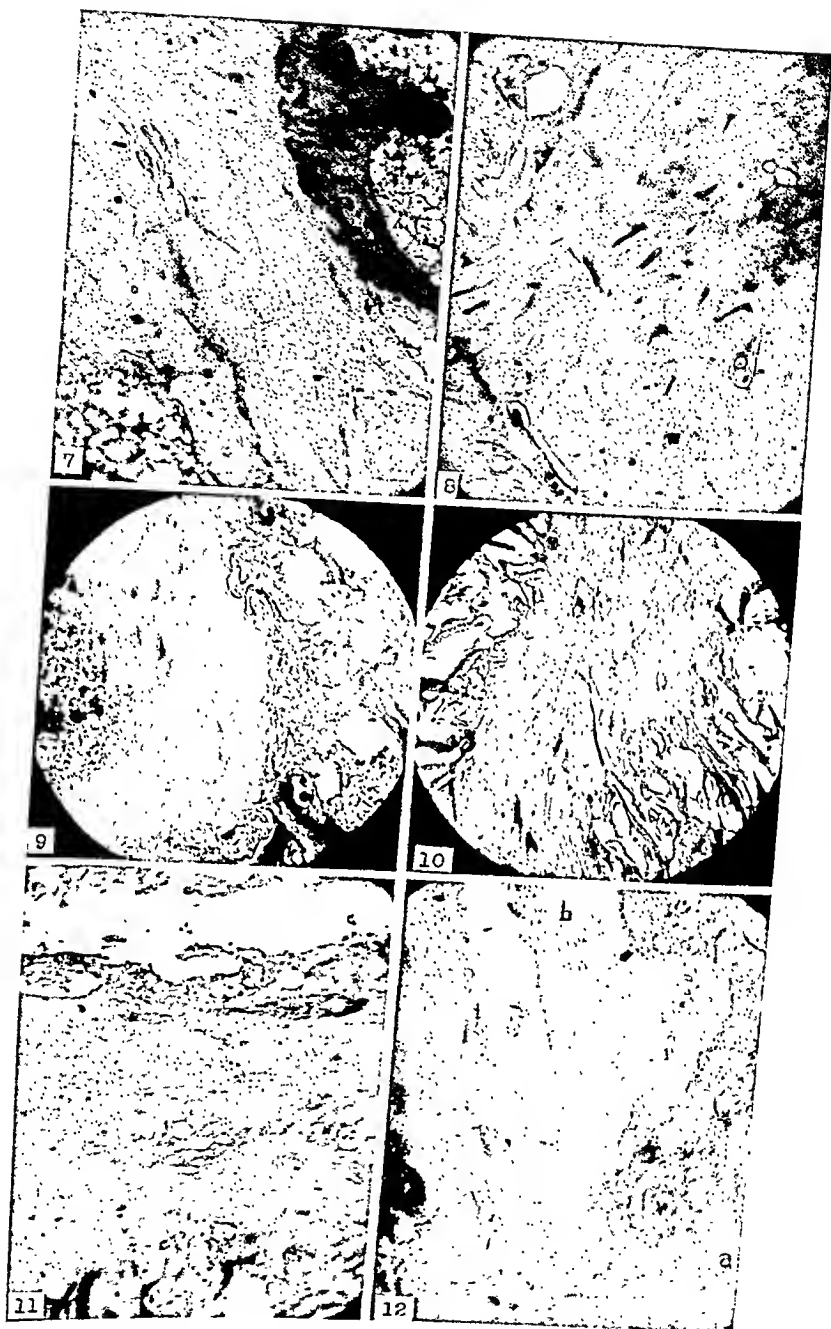
There was apparently firm union on both sides on May 25, 1937.

On June 17, 1937 (6½ months after the first operation and two months after the second operation), the dog was killed, and a specimen was removed from each elbow. Examination showed a wide separation of the fragments on the left side and fibrous union on the right side. X-ray of the specimens showed nonunion on the left side (Fig. 6), and incomplete union with some callus thrown out on the right side (Fig. 5). Microscopic sections of the left elbow showed the fascia intact running through the bone and across the defect between the separated fragments. Sections from the right elbow showed osteoid tissue between the fragments and osteoid cells in the fascia running through the bone.

EXPERIMENT K17 (Dec. 19, 1936).—*Living Fascia in Olecranon*: The left olecranon was exposed, sawed in two, and sutured in the usual manner with a strip of fascia lata removed from the thigh of the same dog. The wound was closed, and a cast was applied.

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Figs. 1 to 6.—Fig. 1: K11. Suture of olecranon with living fascia strips. Specimen removed and x-rayed 104 days after operation. Bony union. Fig. 2: K12. Suture of olecranon with preserved fascia. Cast came off in less than three weeks after operation. Specimen removed and x-rayed seven months after operation. No bony union. Fig. 3: K13. Suture of olecranon with living fascia strip. Specimen removed and x-rayed 4½ months after operation. Bony union not complete from an x-ray point of view, although clinically and microscopically (Fig. 8) there was good bony union. Fig. 4: K14. Suture of olecranon with preserved fascia lata. Specimen removed and x-rayed 27 days after operation. Partial bony union. Fig. 5: K15. Suture of right olecranon with preserved fascia lata strip. Specimen removed and x-rayed 3 months after operation. Some callus thrown out. Microscopic section of this specimen showed osteoid tissue between the fragments and osteoid cells in the fascia running through the bone. Fig. 6: K15. Suture of left olecranon with living fascia strip. Specimen removed and x-rayed 6½ months after operation. Nonunion, presumably due to poor immobilization. Microscopic sections of this specimen showed the fascia intact running through the bone and across the defect between the separated fragments.



Figs. 7 to 12.—Fig. 7: K11. Photomicrograph showing living fascia strip in drill hole in bone 104 days after operation. No ossification of fascia. X-ray (Fig. 1) shows bony union. Fig. 8: K13. Photomicrograph of specimen shown by x-ray in Fig. 1. The implanted fascia has largely been replaced by osteoid tissue. Fig. 9: K11. Photomicrograph of specimen shown in Fig. 1, showing osteoid cells in fascia strip. Fig. 10: K17. Photomicrograph of specimen shown in Fig. 13, showing osteoid tissue in fascia. Fig. 11: K18. Photomicrograph of specimen shown in Fig. 11, showing osteoid tissue and fascia. Fig. 12: K25. Microscopic section of specimen shown in Fig. 13. Note osteoid tissue between fragments (a) and also the fascia in the drill holes (b).

On Jan. 14, 1937 (26 days after operation), the dog died. He was apparently getting good union, but union was not complete. X-ray showed beginning of bony union (Fig. 13). Microscopic sections showed osteoid tissue between the fragments and also in the fascia strips running through the bone (Fig. 10).

EXPERIMENT K18 (Dec. 19, 1936).—*Preserved Fascia in Olecranon*: The right olecranon was exposed, sawed in two, and sutured in the usual manner, using a piece of alcohol-preserved fascia lata removed from the animal in experiment K17. The wound was closed, and a cast was applied.

On Jan. 27, 1937 (39 days after operation), the dog died. A specimen was removed, and x-ray showed no union (Fig. 14). Microscopic sections showed osteoid tissue between the fragments, but more osteoid tissue in the fascia running through the drill holes in the bone. The original fascia could be seen encroached upon on all sides by osteoid tissue (Fig. 11).

EXPERIMENT K19 (Jan. 21, 1937).—*Living Fascia in Olecranon*: The left olecranon was exposed, sawed in two, and sutured in the usual manner with a strip of autogenous fascia lata from the left thigh. The wound was closed, and a cast was applied.

On Jan. 23, 1937, it was discovered that the cast had come off the previous day. Another cast was applied. There was considerable swelling of leg, but wound looked well.

The dog was examined on March 20, 1937. Fragments were nicely approximated, but there was some motion.

April 15, 1937.—*Preserved Fascia in Olecranon*: The right olecranon was exposed, sawed in two, and sutured in the usual manner, with a strip of alcohol-preserved dog fascia lata. The wound was closed, and a cast was applied.

The dog was examined on May 25, 1937. There was firm union on the left side and apparently firm union on the right side.

On June 17, 1937 (5 months after first operation and 2 months after second operation), the dog was killed, and specimens were removed. There was possibly slight motion on the left side, but none on the right. X-ray showed bony union of both sides (Figs. 15 and 16). Microscopic sections of left elbow showed osteoid tissue between the fragments, but the drill holes were not shown in the section. Sections of right elbow showed osteoid tissue present, but it was not clear whether it was in the drill holes, or between the fragments.

EXPERIMENT K20 (Jan. 23, 1937).—*Preserved Fascia in Olecranon*: The right olecranon was exposed, sawed in two, and sutured in the usual manner with a strip of alcohol-preserved fascia lata removed from animal in Experiment K19 on Jan. 21. The wound was closed, and a cast was applied.

On Feb. 27, 1937 (35 days after operation), the dog died, and a specimen was removed by the laboratory technician. X-ray showed bony union (Fig. 17). Microscopic sections showed osteoid tissue between the fragments. The fascia in the drill holes was still present unchanged and showed no osteoid tissue.

EXPERIMENT K24 (Dec. 23, 1937).—*Ox Fascia in Olecranon*: The right olecranon was exposed, sawed in two, and sutured in the usual manner with a preserved strip of ox fascia lata (commercially prepared).<sup>\*</sup> The wound was closed, and a cast was applied.

The dog was examined on Jan. 27, 1938. Fragments were in apposition, and apparently good union was in progress.

On March 10, 1938 (76 days after operation), a specimen was removed. Firm bony union was found on gross examination. X-ray showed firm bony union, with apparently beginning calcification of the fascia strips going around the olecranon (Fig. 18).



13



14



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16



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Figs. 13-19.—See opposite page for legend.

EXPERIMENT K25 (March 19, 1938).—*Ox Fascia in Olecranon*: The right olecranon was exposed, sawed in two, and sutured in the usual manner with a strip of preserved ox fascia lata (commercially prepared),\* which had been removed from the tube in which it had been put up and soaked in 70 per cent alcohol since Dec. 16. The wound was closed, and a cast was applied.

On May 7, 1938 (49 days after operation), the dog was killed. Gross examination showed good bony union. X-ray also showed bony union (Fig. 19). Microscopic sections showed osteoid tissue between the fragments and also in the fascia in the drill holes (Fig. 12).

#### DISCUSSION

In these experiments, where conditions were similar, the fate of living fascia strips and preserved fascia strips when implanted in bone was exactly the same. In suture of the olecranon both with living and preserved fascia strips bony union was obtained in all of the cases where immobilization was completed during the healing process. In our first experiments we did not apply casts and found that invariably we got fibrous union with both types of fascia. In the later cases in which we obtained fibrous union, it always occurred in instances in which we were not able to keep the cast on for the proper length of time. (Dogs tend to chew their casts off, and it is often difficult to keep casts on them.)

Both the living and preserved fascia strips used as suture material in bone underwent ossification at variable periods of time, the earliest time observed being twenty-six days. It is probable that the process begins much earlier than this. It seems that the better the fragments are apposed and immobilized, the earlier ossification takes place. In one case in which living fascia had been used as suture, and in which there was poor immobilization with consequent nonunion, the fascia strip was present unchanged in the drill holes five months after operation, and, in a similar case in which preserved fascia had been used, it was present unchanged seven months after operation.

In cases in which fascia was placed in bone, but given little or no function to perform (Experiments K1, K2, and K3), there was no ossification whatsoever, and almost complete absorption of the fascia

\*Johnson & Johnson, New Brunswick, N. J.

Figs. 13 to 19.—Fig. 13: K17. Suture of olecranon with living fascia lata strip. Specimen removed and x-rayed 26 days after operation. Apparently getting good union, though not yet complete. Fig. 14: K18. Suture of olecranon with preserved fascia lata strip. Specimen removed and x-rayed 39 days after operation. Apparently no union, although microscopic sections showed osteoid tissue between the fragments and more osteoid tissue in the fascia running through the drill holes in the bone. Fig. 15: K19. Suture of right olecranon with preserved fascia lata strip. Specimen removed and x-rayed 2 months after operation. Bony union. Microscopic sections confirm this. Fig. 16: K19. Suture of left olecranon with living fascia strip. Specimen removed and x-rayed 5 months after operation. Bony union. Microscopic sections confirm the diagnosis. Fig. 17: K20. Suture of olecranon with preserved fascia lata strip. Specimen removed and x-rayed 35 days after operation. Bony union. Microscopic sections confirm this. Fig. 18: K24. Suture of olecranon with ox fascia lata (commercially prepared). Specimen removed and x-rayed 76 days after operation. Bony union. Fig. 19: K25. Suture of olecranon with ox fascia lata (commercially prepared). Specimen removed and x-rayed 19 days after operation. Bony union.

(both living and preserved) in comparatively short periods of time. This is not in accord with the conclusions of Kernwein, Fahey, and Garrison,<sup>4</sup> who state that "lack of function had no demonstrable effect" on the fate of fascia in bone. However, it is in accord with the conclusions of Rehn,<sup>6</sup> and of Lewis and Davis,<sup>7</sup> published in 1910 and 1911 respectively. These authors demonstrated that grafts of tendon and fascia behave quite differently when they are given a function to perform than when they are simply implanted into subcutaneous tissue. When given a function to perform, they do not show any tendency to be absorbed. When implanted in subcutaneous tissue, they rapidly decrease in size, do not readily have the circulation re-established, and become surrounded by phagocytes and round cells. This work was not done with bone, but our experiments would seem to indicate that fascia behaves in the same way in bone, so far as absorption is concerned, as it does elsewhere.

#### CONCLUSIONS

1. Good results were obtained in suturing fractures of the olecranon in dogs, using both living and alcohol-preserved fascia strips, provided the parts were properly immobilized.

2. No distinction could be made between the results obtained in the two types of fascia used, either functionally, or in so far as shown by gross, microscopic, and x-ray examinations.

3. Ossification of both types of fascia, by replacement of fascia by ingrowing bone, occurred as union of the fragments was accomplished.

4. In cases in which immobilization was incomplete, resulting in fibrous union, both types of fascia were found intact months after implantation.

5. When fascia (both living and preserved) was implanted in bone, with no function to perform, rapid absorption took place.

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## STUDIES ON SHOCK\*

### III. VARIABILITY OF THE SHOCK SYNDROME IN TOXIC DRUG SHOCK

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WE HAVE been interested in the condition of hemorrhage and shock and its treatment by various infusions.<sup>1, 2</sup> Animal experiments were performed in which profound shock was produced by various means. The main criteria employed in determining and evaluating the severity of shock were low blood pressure, acidosis, as expressed by blood CO<sub>2</sub>, and hemoconcentration, as expressed by hemoglobin values. The blood pressure reflects the state of vasomotor tone, the blood CO<sub>2</sub> the state of tissue oxygenation (and indirectly the adequacy of the peripheral circulation), and the hemoglobin values indicate the plasma-cell ratio and changes in the degree of capillary permeability. In non-anesthetized animals the additional clinical symptoms of prostration, labored respiration, defecation, urination, etc., were recorded. We were impressed by the observation that an animal could present the typical clinical picture of shock without the presence of all three criteria stated above; also that no one of these criteria by itself could be expected to indicate the presence or degree of shock. Moon,<sup>3</sup> in his recent monograph, defines shock as "a circulatory deficiency not cardiac nor vasomotor in origin, characterized by a decreased volume of blood, reduced cardiac output (volume flow of blood), and by hemoconcentration" (page 187), and at another point makes the statement that "hemoconcentration is the earliest detectable manifestation of shock as well as the most accurate index of its severity" (page 184). Our experience did not confirm this point. In a number of experiments we observed that no appreciable hemoconcentration occurred despite death of the animal from experimental shock; whereas, in other experiments definite hemoconcentration developed during shock and yet the animal recovered from a state which might be classified as extremely severe when judged by the degree of hemoconcentration.

We employed various drugs in order to produce shock: histamine,<sup>4</sup> peptone,<sup>5</sup> croton oil, and anesthesia.<sup>6</sup> There was no constancy in the effects of the above drugs when used on anesthetized and unanesthetized dogs,<sup>7</sup> nor was there any constant correlation between the dose of the drug and the production of shock in the individual animal in our forty-six experiments.

#### METHODS

Dogs varying in weight from 10 to 25 kg. were employed. In one group of animals the right carotid artery was cannulated under light ether anesthesia for the purpose of obtaining blood samples and recording blood pressure.<sup>1</sup> Several hours

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TABLE 1

EX- PERI- MENT NO.	DOG WEIGHT (KG.)	INITIAL VALUES			ANES- THESIA	AGENT USED TO PRODUCE SHOCK†	FINAL VALUES				HEMO- CONCENTRATION		REMARKS
		BLOOD PRES- SURE	ARTE- RIAL CO <sub>2</sub>	HEMO- GLOBIN SAHLI (%)			INTERVAL SINCE AD- MINISTRA- TION OF AGENT (HR.)	BLOOD PRES- SURE	ARTE- RIAL CO <sub>2</sub>	HEMO- GLOBIN SAHLI (%)	DEGREE* CHANGE	% CHANGE	
1	16.3	$\frac{160}{110}$	39.6	113	None	Histamine† 5.5 mg. i.v.	2	$\frac{65}{55}$	8.1	152	4+	+36	Died after drawing of last blood sample
2	22.5	$\frac{160}{110}$	34.8	101	None	Histamine 15 mg. i.v.	3	$\frac{125}{95}$	14.6	132	4+	+31	Survived; marked acidosis and hemoconcentration
3	18.5	$\frac{160}{100}$	34.3	108	None	Histamine 22 mg. i.v.	2.5	$\frac{95}{65}$	20.9	107	0	0	Died 45 min. after drawing last blood sample
4	15.9	$\frac{140}{90}$	37.5	107	None	Histamine 57 mg. i.v.	2.5	$\frac{120}{90}$	24.1	116	+	+ 8	Survived; only moderate ac- idosis; resistant to hista- mine
5	16.3	$\frac{180}{110}$	40.3	95	None	Croton oil 0.08 c.c. i.p.	5	$\frac{145}{130}$	27.9	128	4+	+35	Typical croton oil shock; died next morning
6	13	$\frac{155}{100}$	34.4	95	None	Croton oil 0.05 c.c. i.p.	5.5	$\frac{140}{100}$	25.9	120	3+	+26	Hemoconcentration main change; dead next morning

7	19.1	165 110	44.2	101	None	Craton oil 0.15 c.c. i.p.	12	140 105	43.2	128	3+	+27	Hemoconcentration only; survived.
8	10.9	175**	41.6	80	Nembutal	Peptone † 25 Gm. i.v.	1.25	50**	7.7	101	3+	+26	Typical peptone shock; died 3¼ hr. later
9	13.2	150**	44.3	84	Nembutal	Peptone † 40 Gm. i.v.	4.5	120**	16.6	124	4+	+48	Blood pressure fell to 50 and rose to 120 despite marked acidosis and hemo- concentration; killed after 5.5 hr.
10	12.3	155**	42.3	88	Nembutal	Peptone † 34 Gm. i.v.	5.5	70**	13.7	92	0	+4	Profound acidosis and low blood pressure, yet dog lived 6 hr. in such pro- found shock without any hemoconcentration
11	10.9	160**	50.4	84	Nembutal	Peptone † 38 Gm. i.v.	8	90**	19.5	100	2+	+19	Marked acidosis; no parallel change in blood pressure and hemoconcentration after 8 hr.; dead, 10 hr.
12	15.9	135**	58.1	80	Nembutal	None	6.5	90**	42.3	108	4+	+35	Both dogs survived; hemo- concentration most marked change
13	14.1	160	57.8	92	Nembutal	None	8.25	115	42.9	111	3+	+21	

\* Hemoconcentration is graded from 0 to 4+, depending on the percentage increase from the initial value.

† Histamine HCl.

‡ i.v., Intravenously; i.p., Intraperitoneally.

§ Merck.

\*\* Mean pressure.

were allowed to elapse for recovery, so that unanesthetized dogs were used. In another group all experiments were done on dogs anesthetized with sodium pentobarbital or morphine-ether. Histamine and peptone, dissolved in small quantities of saline solution, were injected intravenously. The croton oil was suspended in olive oil and administered intraperitoneally.

### RESULTS

Table I summarizes data of representative experiments. The results are arranged according to the agent employed to produce shock. Histamine and croton oil were given to unanesthetized dogs and blood pressure was measured with a tycoos anaeroid gauge by means of which systolic and diastolic levels were recorded; other experiments were done under anesthesia and the mean arterial pressure recorded (mercury manometer). Anesthesia per se may cause the development of the shock syndrome,<sup>6</sup> necessitating a series of control experiments with sodium pentobarbital or morphine-ether anesthesia only.

Experiments 1 and 8 represent the typical shock syndrome; following administration of histamine or peptone, blood pressure and arterial  $\text{CO}_2$  fell progressively while hemoglobin values rose until death. On the other hand, the animals in Experiments 3 and 10 died in shock and, yet, no hemoconcentration occurred. In Experiments 6 and 7 marked hemoconcentration resulted without particular fall in blood pressure or arterial  $\text{CO}_2$ . In Experiment 4 blood pressure and hemoglobin were not appreciably altered in the presence of profound shock, wherein acidosis was the outstanding feature. In Experiment 11 marked acidosis occurred early, and only as the experiment progressed did blood pressure fall and a moderate hemoconcentration appear.

### DISCUSSION

Histamine and peptone are powerful capillary poisons, paralyzing capillary tone and increasing the area of the vascular bed. Histamine would seem to be the ideal agent for the production of shock. It is a pure substance which can be given in concentrated and accurate amounts. Yet, the results obtained with dogs were extremely variable; one animal would pass into a state of profound shock from a given dose of histamine; another scarcely would be affected. Efforts to produce comparable degrees of shock by repeated doses or constant injection of histamine also failed, for the results were inconstant. In the "histamine experiments" listed in Table I, all dogs were in profound "shock" after the injection of histamine, but the subsequent course and outcome were extremely varied.

Peptone was even more unreliable in its action than histamine. In some animals moderate doses did not cause shock, while large doses often resulted in an irreversible and incurable\* degree of shock.

One would expect the injection of such large doses of both histamine and peptone to cause hemoconcentration since they produce dilatation

\*Results of fluid therapy in shock will be reported separately.

and increased permeability of the capillaries and consequent loss of plasma from the circulation. However, in these experiments the extent of hemoconcentration varied between 0 and 4+\* and bore no constant relationship to the severity of the shock. Death at times occurred without evidence of hemoconcentration at any stage in the development or progress of the shock syndrome. Hemoconcentration was not a reliable or constant feature of shock in our experience.

Doses of croton oil above 0.05 c.c. given intraperitoneally had an intensely irritative effect upon the peritoneum, producing first a copious serous and later an actual hemorrhagic exudate. The effects of this exudation were reflected in the hemoconcentration present in all of these experiments. In all experiments with croton oil the blood pressure began to drop only terminally. A moderate degree of acidosis occurred in experiments 5 and 6; none was noted in Experiment 7.

Nine control experiments were performed in which dogs were anesthetized with sodium pentobarbital or morphine-ether in order to determine the effects of these agents per se on the dogs. Only two of these animals developed shock and died as a result of anesthesia. Hemoconcentration developed in all cases, and, although alkali reserves fell moderately, acidosis appeared only in the two animals which expired.

#### SUMMARY AND CONCLUSIONS

1. The production of shock by histamine, croton oil, and peptone is extremely variable both in anesthetized and unanesthetized dogs.

2. No correlation seems to exist between the degree of shock and dosage of drug employed in different dogs.

3. Even when profound shock is produced, changes in blood pressure, alkali reserve, and extent of hemoconcentration vary widely from experiment to experiment.

4. Profound or even fatal capillary shock may occur without the development of hemoconcentration at any stage of its course.

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\*See Table I.

## STAPHYLOCOCCIC SEPTICEMIA

### TREATMENT BY CHEMOTHERAPY AND SEROTHERAPY

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INVASION of the blood stream by the staphylococcus is a very serious, though infrequent, condition. Reported mortality rates vary between 66 per cent<sup>1</sup> and 91.4 per cent,<sup>2</sup> and Reimann,<sup>3</sup> reviewing large groups of cases, strikes an average of 79 per cent. Recent reports<sup>2, 4-10</sup> of the use of newer therapeutic agents seem to give promise of lowering these figures. Five patients with staphylococcus bacteremia have been under the care of one of us (S. L. G.), 1 in 1934, 1 in 1936, and 3 in 1939 (Cases 1, 23, 27, 29, and 30). These have all survived. The other 3 patients with this condition treated at Michael Reese Hospital in 1939 also survived. These encouraging results, as well as the recent promising reports, prompted us to review all the instances of staphylococcus septicemia treated at the hospital during the years 1934 to 1939, inclusive.

This series includes 32 cases\* of staphylococcemia, 19 males and 13 females, in which 14 died. The total mortality was 43.95 per cent (Table I). In each the diagnosis was established by recovery of the organism from the circulating blood stream in pure culture at least once. Twenty-six were *Staphylococcus aureus*, and 6 were *Staphylococcus albus*. In 23 patients it was recorded that the organism was also recovered from the primary or metastatic focus or both.

The condition is not very common. This is borne out by the incidence of only 32 known and proved cases from a total of 98,825 admissions to the hospital over a six-year period. There can be little doubt, however, that the occurrence of staphylococcus bacteremia is much more frequent than is commonly believed. The great majority of osteomyelitis probably follows bacteremia, and it is not unlikely that some patients with multiple furunculosis also have bacteremia, very transient though it may be. Staphylococcus septicemia is encountered less frequently than the streptococcal variety. Stevens<sup>11</sup> gives the ratio of 2:3; Rosenow and Brown,<sup>1</sup> as 1:2; Mendell,<sup>12</sup> as 1:2.3. The mortality, however, has usually been reported higher than that from streptococcus septicemia, and in our

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experience the duration and the pyemic complications have made the staphylococcic type the one to be dreaded.

One must assume that the natural defense against such a prevalent organism must be very efficient in order to prevent more frequent invasion of the blood stream. The skin and upper respiratory tract are constantly exposed and are subject to frequent subminimal infections through minute abrasions. It has been demonstrated that painting the pharynx with staphylococci or their toxins promotes the formation of antitoxic substances in the body.<sup>13</sup> These are probably the usual means by which a certain antitoxic titer is maintained in the human being. Reichel<sup>14</sup> has shown in experimental animals that, after intravenous injections of *Staphylococcus aureus*, the body defense mechanism can rapidly sterilize the blood stream.

According to Stookey and Scarpellino,<sup>2</sup> the exotoxin elaborated by the staphylococcus can be broken up into several factors, leucocidin, hemolysin, coagulase, a dermonecrotic element, and a lethal toxin. The injection of small amounts (0.5 to 1 c.c. per kilogram of body weight) of this toxin is sufficient to kill experimental animals. These factors of the exotoxin probably account for the sequence of events in invasion of the blood stream through the medium of mycotic emboli arising from the primary focus, and possibly reinvasion from the metastatic foci elsewhere in the body. The amount of toxin in the circulating blood stream cannot as yet be measured. Parish and his associates<sup>15</sup> described a method of titration of the antitoxic content of the blood and showed experimentally that with the antitoxic level elevated the animals survived injections of lethal doses of toxin. Robertson<sup>16</sup> and Weaver<sup>17</sup> have found titration of the antitoxic level in the blood to be of value clinically, especially in prognosis.

In our series the organism entered the body through various portals, of which the skin was the most frequent. The initial skin lesion may be small enough to evade the most careful search. In 9 of our 32 cases the first focus is recorded as osteomyelitis; these may have been of such an origin. In 14 others the skin focus was known, 11 carbuncles or furuncles, 1 infected bulla, 1 laceration, and 1 infection secondary to trichophytosis of the feet. Upper respiratory tract infection preceded the bacteremia in 6 cases, and in 1 case each the origin was puerperal sepsis, urinary tract infection, and a postoperative infection of a nasoplasty incision.

There was considerable variation in the period of time between the appearance of the initial focus of infection and the manifestations of blood stream invasion. In 4 patients there were early symptoms so alarming as to prompt taking blood for culture within forty-eight hours of the known onset of the initial lesion, and in the rest this period varied

TABLE I  
ALL PATIENTS IN THE SERIES GROUPED ACCORDING TO THERAPY USED

NO.	DATE	AGE	SEX	SITE OF ORIGINAL LESION	BACTERIAL CULTURES		ASSOCIATED OSTEO-MYELITIS	CLINICAL COURSE	RESULT	PER CENT MORTALITY
					LESION	BLOOD				
<i>Patients Given Supportive Therapy</i>										
1	March, 1934	45	M	Tricophytosis feet	?	Aureus		Protracted	Recovered	37.5
2	August, 1934	15	M	Osteomyelitis	Albus	Albus	+	Protracted	Died	
3	August, 1934	2	F	Osteomyelitis	Aureus	Aureus	+	Moderately severe	Recovered	
4	October, 1934	13	M	Osteomyelitis	Albus	Albus	+	Moderately severe	Recovered	
5	March, 1935	24	M	Upper respiratory		Aureus	+	Moderately severe	Recovered	
6	November, 1935	68	F	Perineal abscess	?	Albus		Protracted	Died	
7	December, 1937	48	F	Carbuncle on forehead	Aureus	Aureus		Protracted	Died	
8	January, 1938	3 wk.	M	Osteomyelitis	Aureus	Aureus	+	Benign	Recovered	
<i>Patients Treated With Sulfanilamide</i>										
9	July, 1937	61	M	Carbuncle	Aureus	Aureus		Fulminating	Died	100.0
10	August, 1937	22	M	Upper respiratory		Albus		Fulminating	Died	
11	November, 1937	30	F	Puerperal	?	Aureus	+	Fulminating	Died	
12	May, 1938	10 mo.	M	Osteomyelitis	Aureus	Aureus		Fulminating	Died	
13	May, 1938	1 mo.	M	Furuncle	Albus	Albus		Fulminating	Died	
14	July, 1938	66	M	Urinary tract	Aureus	Aureus		Protracted	Died	

*Patients Treated With Sulfanilamide and Antitoxin*

Patients Treated in the Study											
15	July, 1937	6	F	Carbuncle on scalp	Aureus	Aureus	Aureus	+	Moderately severe	Recovered	33.0
16	February, 1938	20	F	Carbuncle on neck	Aureus	Aureus	Aureus	+	Protracted	Died	
17	April, 1938	8	M	Furuncle	Aureus	Aureus	Aureus	+	Moderately severe	Recovered	
18	February, 1938	12	F	Upper respiratory	Aureus	Aureus	Aureus	+	Moderately severe	Recovered	
19	December, 1938	14	F	Bulla toe	Aureus	Aureus	Aureus	+	Fulminating	Died	
20	September, 1938	50	F	Traumatic laceration	?	Aureus	Aureus	+	Benign	Recovered	

*Patients Treated With Antitoxin*

21	April, 1936	14	M	Upper respiratory	Aureus	Aureus	Aureus	+	Fulminating	Died	
22	July, 1936	27	M	Furuncle on forehead	?	Aureus	Aureus	+	Fulminating	Died	
23	December, 1936	8	F	Upper respiratory	Aureus	Aureus	Aureus	+	Protracted	Recovered	50.0
24	November, 1937	12	M	Upper respiratory	Aureus	Aureus	Aureus	+	Moderately severe	Recovered	
25	July, 1938	10	M	Osteomyelitis	Aureus	Aureus	Aureus	+	Moderately severe	Recovered	
26	September, 1938	4	F	Osteomyelitis	Aureus	Aureus	Aureus	+	Protracted	Died	

*Patients Treated With Sulfapyridine*

27	February, 1939	2	F	Osteomyelitis	Aureus	Aureus	Aureus	+	Benign	Recovered	0
28	May, 1939	11	M	Osteomyelitis	Aureus	Aureus	Aureus	+	Moderately severe	Recovered	
29	December, 1939	12	F	Osteomyelitis	Aureus	Aureus	Aureus	+	Moderately severe	Recovered	

*Patients Treated With Sulfapyridine and Antitoxin*

30	February, 1939	10	M	Carbuncle on neck	Aureus	Aureus	Aureus		Fulminating	Recovered	0
31	April, 1939	24	F	Nasopharynx	?	Aureus	Albus		Fulminating	Recovered	
32	June, 1939	2	M	Furuncle on nose	Aureus	Aureus	Aureus		Fulminating	Recovered	



## CLINICAL PICTURES AND CASE REPORTS

The clinical pictures merit some detailed description, though in many respects they followed the patterns previously described by many authors. All patients have had temperatures; the ones who died invariably had temperatures above 104°. Toxemia was evident in all, marked in many. Chills were common and severe.

Three patients had a surprisingly benign clinical course, with symptoms that were not pronounced, and relatively low temperatures. An example of this is Case 20 (Fig. 1).

CASE 20.—A 50-year-old female was admitted to the hospital on Sept. 29, 1938. She had sustained a laceration of her right leg three weeks previously, and it had healed rapidly and uneventfully. On the day before admission her temperature rose to 102°\* and she complained of pain in the right iliac region and in her left hip. There were no abnormal physical findings except tenderness in these areas. The pain and fever persisted, and on Sept. 30, because of the history, symptoms, and indeterminate fever, blood was drawn for culture. Hemolytic *Staphylococcus aureus* was recovered in pure culture. Sulfanilamide was given, 120 gr. in twenty-four hours for four days, and the dose was then reduced to 80 gr. in twenty-four hours. There was little change in the clinical picture. On Oct. 14 the blood sulfanilamide level was 4 mg. per 100 c.c. On Oct. 6 and 9 *Staphylococcus aureus* was again grown in pure culture from the blood. On Oct. 12, 40,000 units of staphylococcus antitoxin were given intramuscularly. Transient urticaria followed. On Oct. 17, 60,000 units of staphylococcus antitoxin and 600 c.c. of blood were given intravenously. This was followed by some improvement in the general condition and a reduction in temperature to about 101°. On Oct. 17 and 27 staphylococci were again reported grown in pure culture from the blood. During this period there was slow but gradual improvement, and on Nov. 7 culture of the blood proved sterile. The temperature dropped to normal by lysis, and on Nov. 12 the patient was well enough to be sent home.

The clinical course in ten patients was moderately severe, with temperatures of at least 102 to 103°, toxemia, and mild anemia. These require no detailed reports. The course in the 19 severely ill patients was fulminating in 11 and protracted in 8. Two examples of fulminating infections merit report in some detail.

CASE 31.—(Fig. 2.) A 24-year-old female had a nasal plastic repair on April 18, 1939. Forty-eight hours later her temperature rose to 101.2° R., and she had severe pain at the site of operation. There was some diffuse swelling and redness of the nose. Sulfanilamide was given in 15 gr. (1 Gm.) doses four times daily. The temperature rose gradually, reaching 103.4° on April 26. At this time *Staphylococcus albus* in pure culture was reported grown from blood taken for culture on April 24. On April 26 she had a chill; her temperature rose to 105° and she was much more toxic. The dosage of sulfanilamide was increased to 120 gr. (6 Gm.) daily, but the toxicity and temperature persisted, temperature readings reaching 105° on April 28 and 29. Blood sulfanilamide levels were 4 mg. per 100 c.c. on April 27, and 6.6 mg. per 100 c.c. on April 28. On April 29 a repeat culture of the blood

\*All temperatures are in degrees Fahrenheit and were taken by rectum.

again revealed *Staphylococcus albus*. At this time the administration of sulfanilamide was stopped, and sulfapyridine was given in doses of 30 gr. (2 Gm.) every four hours. On April 30, 100,000 units of staphylococcus antitoxin were given intravenously. That night her temperature rose to 106° and then dropped to normal, where it remained. On May 1 blood sulfapyridine was 6.2 mg. per 100 c.c. After one week of normal temperature, the patient left the hospital on May 7, fully recovered. At no time was there more than a slight serous discharge from the wound.

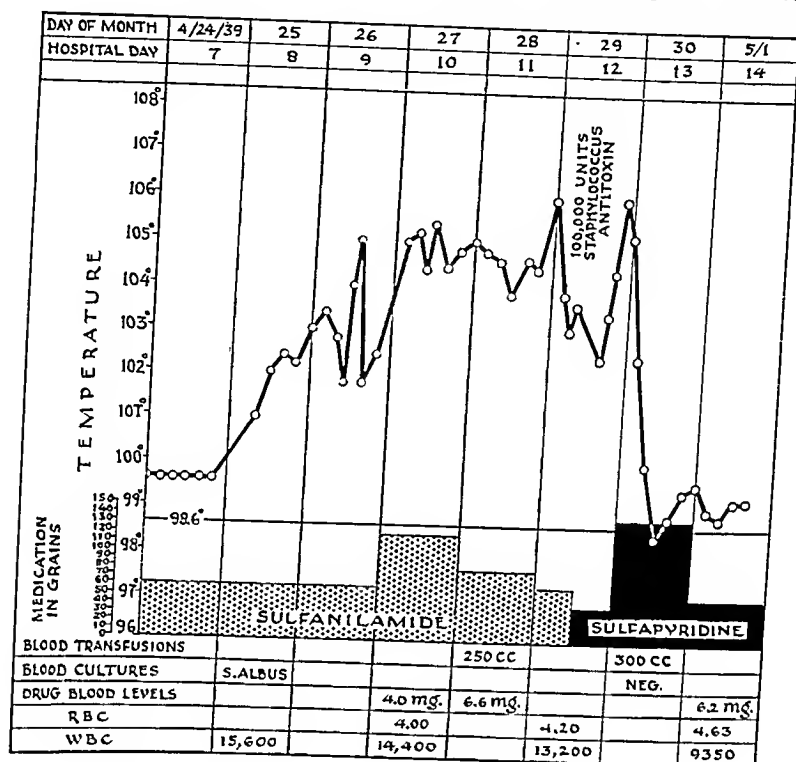


Fig. 2.—Temperature, laboratory data, and treatment in Case 31.

CASE 30.—(Fig. 3.) A 10-year-old male had a small carbuncle on his neck for one week prior to his admission to the hospital on Feb. 12, 1939. His temperature was 102.8° F., and the family was told that the fever seemed out of proportion to the size and appearance of the lesion. That afternoon, under ethylene anesthesia, crucial incisions were made and frank pus was evacuated. Culture of this pus revealed *Staphylococcus aureus*. In the next twelve hours the patient had three chills, and the temperature rose to 104°. The boy vomited several times and was very toxic, becoming irrational at intervals. His leucocyte count was only 6,900. We felt that we were dealing with a fulminating septicemia, probably staphylococci, and blood was drawn for culture. Vigorous treatment was instituted without delay. He was given 30 gr. (2 Gm.) of sulfapyridine by rectum every four hours. He received 250 c.c. of blood by indirect transfusion, following which a total of 110,000 units of staphylococcus antitoxin was administered intravenously, diluted in saline solution, in the succeeding eight hours. Fifteen minims of adrenalin solution (1:1,000) was given with this because of the patient's known allergy. His temperature reached 106.6° that night, then dropped rapidly to normal, and remained there except for a

slight transient rise two days later. At this time *Staphylococcus aureus* in pure culture was reported grown from the blood. Vomiting stopped promptly, permitting oral administration of 60 gr. (4 Gm.) of sulfapyridine in divided doses daily for the next two days. It was then stopped because of the rapidly improving general condition, the blood sulfapyridine level being 5.1 mg. per 100 c.c. on Feb. 15. There was a rather unpleasant urticaria from the seventh to the tenth day and a daughter furuncle in the neck which was drained, but otherwise the patient's convalescence was uneventful.

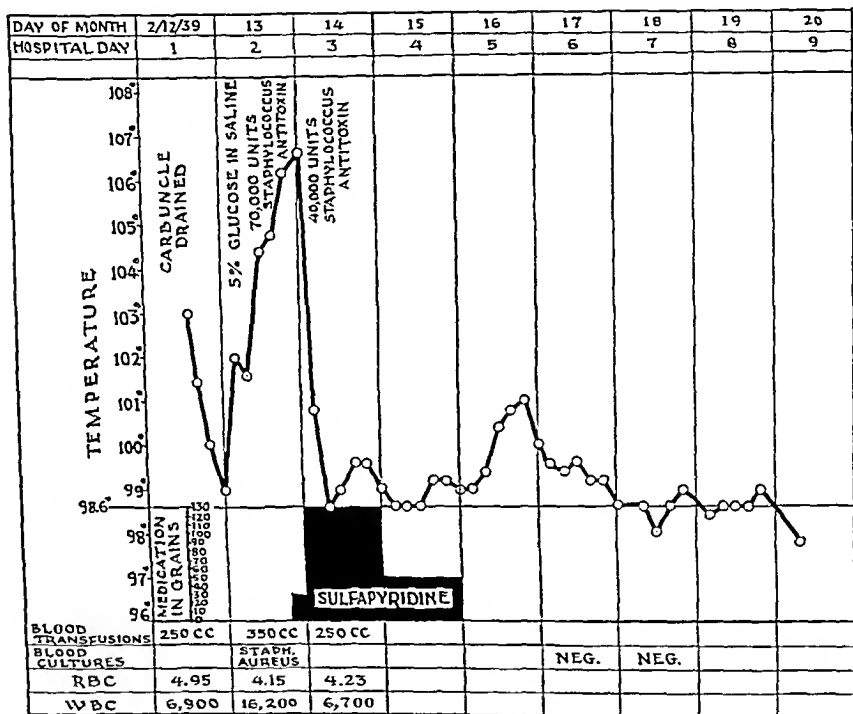


Fig. 3.—Temperature, laboratory data, and treatment in Case 30.

An example of a patient with a severe, protracted clinical course follows:

CASE 23.—An 8-year-old female entered Michael Reese Hospital on Dec. 19, 1936. There was a history of a cold, fever, sore throat, and cervical adenitis for two weeks. On admission she was acutely ill. Her temperature was 102° F.; pulse, 116; and respiration, 28. Her throat was edematous and injected, and there were numerous enlarged, tender, cervical lymph nodes. Examination of the ears, chest, abdomen, and extremities revealed nothing abnormal. Red blood count was 4,000,000; hemoglobin, 80 per cent; and leucocyte count, 30,000. The urine was scant in amount, smoky, and contained albumin. Microscopic examination of the sediment showed eight to ten erythrocytes and two to four leucocytes per high-power field.

During the next few days there was little change in the patient's general condition. The urine became more smoky and then definitely bloody. On Dec. 23 the edematous, bulging parapharyngeal space on the right side was incised, but no

pus was obtained. The temperature ranged between 101 and 104°. On Dec. 24 the patient complained of pain which persisted in the right chest and flank. On Dec. 28 there was induration over the fifth rib in the right anterior axillary line. On Dec. 30 this became fluctuant and was incised. Frank pus was obtained from beneath the periosteum of this rib. *Staphylococcus aureus* was grown in pure culture from the blood drawn on Dec. 28, as well as from the pus from the subperiosteal abscess of the rib.

On Jan. 2, 1937, aspiration of the patient's right pleural cavity confirmed the presence of an empyema, and closed drainage was instituted. *Staphylococcus aureus* was grown from another specimen of blood on Jan. 2. The patient's condition became progressively worse. Perinephritic or liver abscess was suspected because of upper abdominal tenderness and distention and continued hematuria and albuminuria. There was some edema, particularly of the extremities. The temperature was septic in character, ranging from 99 to 105°, and the prognosis seemed almost hopeless. On Jan. 15, 10,000 units of staphylococcus antitoxin were given intravenously. This was followed by an anaphylactic reaction of such severity that no further antitoxin therapy was attempted. By Jan. 17, about six weeks after onset of the illness, a large fluctuant mass localized in the lower abdominal wall. This was incised, and about 300 c.c. of pus was evacuated. There was little change in the desperate general condition for the next several weeks. The patient was given a total of twenty-one small blood transfusions, one every few days, during this critical phase of her illness. On Feb. 16 and 17 examination of the ocular fundi established that the right jugular vein was thrombosed. On Feb. 18 surgical exploration of the vein confirmed the thrombosis; it was ligated, and a section was excised for histologic examination. At the same time the right perinephritic and subphrenic spaces were explored, and multiple miliary abscesses of the liver and right kidney were found. During the next several weeks there was a slight but gradual general improvement. The pulse rate dropped from about 160 to about 140, and the temperature averaged between 102 and 103° instead of between 103 and 104°. The empyema cavity was smaller, but the rib drained profusely and sequestration was evident in the roentgenograms. Hematuria and albuminuria decreased gradually. Blood cultures were repeatedly positive, with the exception of one sterile specimen drawn on Feb. 19. On Feb. 27 blood drawn for culture was sterile, and the blood remained so on several subsequent examinations.

On March 6 the entire necrotic fifth rib was removed, and the small residual empyema cavity was unroofed. After several stormy days definite improvement became noticeable and continued slowly, until on May 4 the child was sent home, although a low-grade temperature and a pulse of about 120 persisted.

In April, 1938, the child was readmitted to the hospital with severe back pain and fever. After two weeks an abscess localized and was drained. *Staphylococcus aureus* was grown in pure culture from the pus. Repeated cultures of the blood were negative. After a protracted course of three months the patient left the hospital. At the present time it seems that the child has made a complete recovery.

#### MORTALITY

The lower mortality rate (25 per cent) in the children under 10 years of age as compared with the adults in our series (Table II) parallels the experiences of other authors, as does the lower death rate (23.5 per cent) in that group of patients with associated osteomyelitis<sup>2, 4, 5, 12, 16, 17</sup> (Table III).

TABLE II  
DISTRIBUTION AND MORTALITY IN VARIOUS AGE GROUPS

AGE	NO. OF CASES	DIED	RECOVERED	PER CENT MORTALITY
Under 1 yr.	3	2	1	66.6
1-10 yr.	9	1	8	11.1
10-20 yr.	8	3	5	37.5
20-30 yr.	5	3	2	60.0
30-40 yr.	1	1	0	100.0
40-50 yr.	2	1	1	50.0
50-60 yr.	1	0	1	0.0
60-70 yr.	3	3	0	100.0
Totals	32	14	18	44.0

There were no deaths in the patients whose clinical courses were relatively benign or moderately severe. On the other hand there were 8 deaths in 11 patients whose clinical courses were severe and fulminating. It is significant that the 3 recoveries in this group (Cases 30, 31, and 32) were the patients who received early and adequate treatment with both sulfapyridine and staphylococcus antitoxin. In the 8 patients whose clinical courses were severe and protracted there were 6 deaths. The 2 patients who recovered received only supportive therapy and are striking illustrations of the fact that even before the advent of specific therapy there were occasional recoveries from this condition. Of the 14 deaths, 9 occurred within two weeks, 3 within two to six weeks, 1 after nine weeks, and in 1 the history of onset was unobtainable.

TABLE III  
MORTALITY IN CASES WITH AND WITHOUT OSTEOMYELITIS

	TOTAL	RECOVERED	DIED	PER CENT MORTALITY
Osteomyelitis	17	13	4	23.5
Nonosteomyelitis	15	5	10	66.6

Associated diseases, of course, exert an unfavorable influence on recovery. In our series the following complicating conditions were encountered: syphilis in 2 instances, diabetes mellitus in 3, renal infection and urosepsis in 1, and marked arteriosclerosis and coronary sclerosis in 1. In the group of patients with these diseases the mortality, as might be expected, was high (80 per cent).

#### TREATMENT

Observation and study of the clinical course of the patients in our series lead us to believe that, although staphylococcus septicemia is a serious illness, there are some patients who recover without specific therapy and other patients who will die in spite of any therapy known at the present time. The majority of cases probably fall in a group that

are amenable to newer methods of specific therapy and may not have been benefited by older methods of nonspecific supportive treatment.

It has been very interesting to follow the trend in the treatment of staphylococcus bacteremia during the past few years. Until several years ago treatment was mainly supportive. In our series 8 patients received only supportive therapy. The mortality rate was 37.5 per cent (Table I) in this group. This figure cannot be compared with those in other reports because of the small number of cases in our study. Supportive treatment consisted of rest, sedatives, adequate fluids given orally, parenterally, or both, blood transfusions to transfer antibodies as well as to combat anemia, and attempts at chemotherapy with various dye antiseptics. Treatment of local lesions by rest, heat, and incision and drainage of collections of pus, of course, was carried out. Associated disease processes were treated; e.g., diabetes mellitus, syphilis, renal disease, etc.

In our series various other types of treatment were used, some specific, some nonspecific. These included, among others, tin preparations, staphylococcus toxoid, bacteriophage, and transfusions of blood from immune donors. There have been several case reports claiming beneficial effects following the use of toxoid and bacteriophage. It is impossible to draw any conclusions regarding their efficacy because of their limited use. Theoretically, blood transfusions from immune donors, if available, might be beneficial in the severely ill patients. In contrast to our experiences and results with the use of immune human serum or blood in streptococic septicemia,<sup>12</sup> we observed no striking or encouraging results following our limited use of immune human blood in staphylococic septicemia. Furthermore, the difficulty of obtaining such blood in sufficient quantities is great enough to render such therapy impractical, especially inasmuch as specific immune bodies are readily obtainable in the form of commercial antitoxin.

With the advent of sulfanilamide, this drug was employed in the treatment of staphylococcus septicemia with the hope that it would be of as much value as it is in the streptococcus infections. Sulfanilamide alone was used in treating 6 patients. All of these cases terminated fatally. Six other patients were treated with sulfanilamide in combination with staphylococcus antitoxin, and, of these, 4 recovered (Table I). It did not appear to us that sulfanilamide had any specific value in the treatment of staphylococcus septicemia. Several isolated instances of recovery following its use have been reported. Most of these patients had clinical courses that were either moderately severe or protracted, in which groups there is a higher incidence of recovery without the use of specific therapy, as noted previously. The 20th anniversary of this. We do not believe that in this situation we can attribute any specific value to the drug.

Fifteen patients, of whom 11 were 14 years of age or less and 4 more than 14 years old, were treated with staphylococcus antitoxin, either alone, or in combination with sulfanilamide or sulfapyridine (Table IV). Formerly, severe serum reactions following administration of

TABLE IV  
MORTALITY IN CASES TREATED WITH STAPHYLOCOCCUS ANTITOXIN\*

	NO. OF CASES	OSTEO- MYELITIS	NONOSTEO- MYELITIS	MORTALITY		TOTAL MORTALITY
				OSTEO- MYELITIS	NONOSTEO- MYELITIS	
Antitoxin alone	6	4	2	1	2	50.0%
Antitoxin with sul- fanilamide	6	4	2	1	1	33.3%
Antitoxin with sul- fapyridine	3	0	3			0 %
Totals	15	8	7	2	3	33.3%

\*See text for age distribution.

antitoxin deterred us and other physicians from its use. Recent refinements by purification and concentration have reduced the incidence and severity of these reactions. Other authors believe that the use of antitoxin has reduced mortality to about 50 per cent.<sup>2, 4, 5, 19, 20</sup> In our series of 15 cases there was a total mortality rate of 33.3 per cent. In the younger group there were 3 deaths, a mortality of 27.33 per cent; and of the 4 adults 2 died, a mortality of 50 per cent. Our experience, particularly in the more recent cases, where larger doses of antitoxin were employed (100,000 to 180,000 units), leads us to believe that antitoxin is of definite value and that it should be administered early in sufficient dosage. Possibly the use of larger dosages and further improvement in the preparation will increase its effectiveness. The initial dose in adults with severe infections should be at least 100,000 units, following sensitization tests and desensitization where necessary. We used the intravenous route and found that, if the antitoxin is diluted in saline solution, the reactions are not so frequent or severe. It should be given slowly over a period of several hours. In patients with allergic backgrounds or histories of allergic manifestations, adrenalin solution in small doses should be given at the same time. Further administration of antitoxin depends upon the clinical picture. Daily doses should be given, usually in decreasing amounts, until the subsidence of manifestations of the acute phase of the infection.

Sulfapyridine was used in the treatment of all 6 patients with staphylococcus septicemia admitted to the hospital during 1939. In 3 of the patients sulfapyridine was combined with staphylococcus antitoxin. We have reported 2 of these cases,<sup>7</sup> in which a deliberate therapeutic trial of sulfapyridine was made. No other specific therapy was used and both patients recovered. Complete recovery in this group of six consecutive cases (Table I) is very significant.

The initial dose of the drug used was approximately 1.5 grains per pound body weight each twenty-four hours. This dose was continued, maintaining a sulfapyridine level in the circulating blood stream of at least 6.0 mg. per cent, preferably between 6.0 mg. and 9.0 mg. per cent. The drug can be given rectally, and a soluble form is now available for subcutaneous and intravenous use.<sup>21</sup> We have administered it by rectum on several occasions and have found it effective. With subsidence of symptoms, the dose should be gradually reduced.

Mild toxic effects of the drug such as nausea and vomiting are encountered frequently, apparently without relation to the dosage or to the drug blood level. They are probably of central nervous system as well as of gastrointestinal origin.<sup>22</sup> Cyanosis is frequent, especially with high blood levels. Skin rashes and tingling of extremities are also occasionally seen. The more serious manifestations are fortunately less common and are thoroughly discussed in other publications.<sup>22, 23</sup> We have not encountered them in our experience and would not let them deter us from the use of this drug in a disease as severe and fatal as staphylococcus septicemia.

Although our experience with sulfapyridine therapy of staphylococcus septicemia is not extensive, we feel that we can strongly recommend its use. In the 2 cases referred to previously,<sup>7</sup> the control was as adequate as can be exercised in clinical procedure and treatment was followed by rapid sterilization of the blood stream. In all 6 patients, and especially in the 3 patients for whom the use of sulfapyridine was combined with staphylococcus antitoxin therapy, the clinical improvement was very definite and rapid and occurred soon after the institution of treatment.

Undoubtedly further developments in chemotherapy will ensue. Herrell and Brown<sup>10</sup> reported the recovery of a patient following the use of sulfamethylthiazol in a case of staphylococcus sepsis. Fitch<sup>8</sup> reports the recovery of a 10-year-old girl who had a severe, protracted clinical course. Helmholz<sup>24</sup> reported that the drug is bactericidal in vitro to the organisms found in urinary tract infections. These authors and Long<sup>25</sup> think it is at least as efficient as sulfapyridine, and probably less toxic, although it is too early to make accurate comparisons. The future may give us drugs with even more specific action against the staphylococci.

The mode of action of the chemotherapeutic agents and of staphylococcus antitoxin differ. The exotoxin elaborated by the staphylococci are apparently neutralized by antitoxins, while the bacteria themselves are affected by the drugs in a way as yet not fully understood. Multiplication of the organisms is diminished, and they are in some way sufficiently attenuated to allow their destruction by body defenses. It seems, on theoretical grounds, that synergistic action between the two agents might obtain. A definite and parallel synergistic action between sulfapyridine and antipneumococcus serum against the pneumococcus

has been reported.<sup>22, 26, 27</sup> This hypothesis of synergistic action seems to be confirmed by some interesting work reported by De and Basu.<sup>28</sup> They did experimental work on mice employing sulfanilamide, staphylococcus antitoxic serum, and combination of the two agents in protection against staphylococcal infection. A group of mice inoculated with a certain dose of *Staphylococcus aureus* and untreated all died. Another group, likewise infected with the organism, were treated with sulfanilamide, and 33 per cent survived. Twenty-five per cent of another similar group treated with antitoxin survived. There was 100 per cent survival in a fourth group treated with the same doses of both therapeutic agents. All this evidence is strongly suggestive that combined therapy is more effective than either type of therapy used alone. Meyer<sup>29</sup> reports three cases that recovered following treatment with staphylococcus antitoxin and sulfanilamide and believes there is synergistic action between these agents.

Sound surgical treatment of local lesions is paramount. There is general agreement that, if the infection is in soft tissues, it should be treated conservatively and not manipulated until pus is formed. Heat and possibly x-ray therapy are of value in localizing the infection. When there is a collection of pus, it should be evacuated.

There is at present a distinct trend toward a change in the treatment of osteomyelitis. Until several years ago the teaching was general that acute osteomyelitis was a surgical emergency. In order to avoid stripping of periosteum and further bone destruction, drainage was advocated as soon as even a presumptive diagnosis was made. In several recent reports<sup>30-33</sup> delayed operation and more energetic treatment of the general condition of the patient was carried out. The results reported are good. The use of sulfapyridine and staphylococcus antitoxin should further these ideas. Three cases that seem significant<sup>34</sup> have come to our attention very recently. In each there was a very typical clinical picture of acute osteomyelitis, which subsided completely after conservative management by rest, local heat, and sulfapyridine therapy. There were only minimal x-ray findings of bone destruction several weeks later. Up to the present time (between six weeks and three months after onset), these patients are clinically recovered and have not required surgery.

Early diagnosis of staphylococcus septicemia and institution of treatment even before the diagnosis is established by laboratory procedures are important factors in the reduction of mortality. Any rise in temperature or increase in toxicity above what may be expected from any infected focus, particularly when accompanied by chill, should be sufficient grounds for instituting vigorous treatment. The situation can be compared to the treatment of diphtheria and of meningococcus meningitis. In diphtheria vigorous specific treatment is begun when a suspicious membrane is present in the throat, and no time is lost waiting

for positive culture reports. We urge the institution of vigorous specific therapy, without waiting for blood culture reports, as soon as a patient with a known staphylococcus infection, or a recent history of one, develops graver symptoms than can be accounted for by the local lesion. For example, in our Case 30 sulfapyridine, staphylococcus antitoxin, and a blood transfusion were given, and the patient was clinically practically cured before the growth of organisms from culture of the blood was reported.

#### SUMMARY AND CONCLUSIONS

1. *Staphylococcus septicemia* is a condition having a mortality, until very recently, averaging 76 per cent.

2. We are reporting a series of 32 cases with a mortality rate of 44 per cent.

3. As a rule, those cases with an acute and fulminating onset have a higher mortality rate.

4. Of the various types of therapy employed in our series, staphylococcus antitoxin and sulfapyridine gave the most direct evidence of favorably influencing the course of the disease.

5. The last 6 consecutive cases, all in 1939, recovered. All of these received adequate doses of sulfapyridine, and 3 also received staphylococcus antitoxin.

6. There is clinical and experimental evidence to support the tenet that chemotherapy and serotherapy are synergistic in action and that both agents should be used in the treatment of staphylococcus septicemia.

7. Early clinical diagnosis and prompt institution of chemotherapy and serotherapy before corroboration of the diagnosis by blood culture is important.

8. Supportive treatment and sound surgical measures are essential.

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# THE INEFFICACY OF LUMBAR PUNCTURE FOR THE REMOVAL OF RED BLOOD CELLS FROM THE CEREBROSPINAL FLUID

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CONSIDERABLE difference of surgical opinion exists as to the value of lumbar puncture for the removal of red blood cells from the subarachnoid space, whether the hemorrhage occurs spontaneously or post-traumatically. The presence of blood in the cerebrospinal fluid has been definitely shown to have pathologic sequelae by the work of Essick,<sup>1</sup> Weed,<sup>2</sup> Bagley,<sup>3</sup> and Wortis,<sup>4</sup> as pointed out by Lehman and Parker.<sup>5</sup> Most observers, such as Bagley,<sup>6</sup> Fay,<sup>7</sup> Keegan,<sup>8</sup> and Sharpe<sup>9</sup> believe that the removal of relatively large amounts of cerebrospinal fluid will eliminate significant quantities of red blood cells, although a few observers raise doubts as to its real value in this respect (Coleman,<sup>10</sup> Dandy<sup>11</sup>).

However, Sprong,<sup>12</sup> in 1934, in a well-controlled study showed, both in the experimental animal (dogs) and in patients, that the rate of disappearance of erythrocytes from the subarachnoid space is not appreciably affected by the withdrawal of cerebrospinal fluid. He injected blood into the cisterna magna of seven dogs and, at varying periods of time thereafter (up to seven days after injection), he removed all the available cerebrospinal fluid by means of a lumbar laminectomy. He found that, after the first forty-eight hours following injection of blood into the cisterna magna, there was never more than 2 per cent of the entire amount of originally injected erythrocytes recoverable, even when all available spinal fluid was removed by lumbar laminectomy, which is a much more complete drainage than is ever accomplished clinically in the treatment of subarachnoid hemorrhage. Russell<sup>13</sup> has also published (1932) curves of the disappearance of red blood cells from the cerebrospinal fluid in clinical cases which exactly correspond to those of Sprong, although he does not relate them to the amount of fluid removed.

It was considered important to verify the experimental work of Sprong as a careful review of the literature to date, following his publication, revealed no similar study. Lehman and Parker<sup>5</sup> stated that Sprong's work, if confirmed, demonstrates the uselessness of a procedure that a majority of surgeons has been assuming to be of major value.

## METHODS

*A. Experimental.*—With certain minor variations in technique the work of Sprong was repeated in twice the number of dogs. Food and

TABLE I\*

DOD NO.	BLOOD COUNT (MILLION CELLS PER CU. MM.)	C.C. OF BLOOD INJECTED INTO CISTERNA	INTERVAL OF TIME BEFORE DRAINAGE OF ALL CEREBRO- SPINAL FLUID	C.C. OF CEREBRO- SPINAL FLUID OB- TAINED (LUMBAR LUMINEC- TOMY)	CEREBRO- SPINAL FLUID COUNT (R.B.C. PER CU. MM.) (FLUID FROM LUMBAR LUMINEC- TOMY)	TOTAL NO. OF CELLS INTRODUCED ( $\times 10^6$ )	TOTAL NO. OF CELLS RECOVERED ( $\times 10^6$ )	PERCENTAGE OF INJECTED R.B.C. RECOV- ERED IN CEREBRO- SPINAL FLUID	PERCENTAGE OF INJECTED R.B.C. WHICH DISAPPEARED SPON- TANEOUSLY
1	0,360,000	2 c.c.	2 1/2 hr.	8.0	500,000	12,720	4,000	31.4	68.6
2	6,000,000	2 c.c.	4 hr.	9.0	355,000	12,000	3,195	26.6	73.4
3	6,840,000	2 c.c.	2 1/2 hr.	8.5	330,000	13,680	2,805	20.5	79.5
4	6,480,000	2 c.c.	2 1/2 hr.	9.7	325,000	12,960	3,153	24.0	76.0
5	5,000,000	2 c.c.	48 hr.	10.5	58,400	10,000	613	6.1	93.9
6	5,390,000	2 c.c.	3 days	7.0	30,200	10,780	271	1.9	98.1
7	6,000,000	2 c.c.	4 days	15.0	1,000	12,120	15	0.12	99.8
8	9,930,000	2 c.c.	5 days	7.3	125,000	19,860	912	4.5	95.5
9	7,440,000	2 c.c.	6 days	10.5	60,000	14,880	630	4.2	95.8
10	6,060,000	2 c.c.	7 days	9.1	55,000	13,320	500	3.7	96.3
11	7,420,000	2 c.c.	8 days	7.4	25,200	14,840	186	1.3	98.7
12	6,270,000	2 c.c.	0 days	7.5	6,800	12,540	51	0.4	99.6
13	7,640,000	2 c.c.	12 days	7.0	40,000	15,280	280	1.8	98.2
14	7,710,000	2 c.c.	21 days	7.5	3,500	15,420	26	0.16	99.84

\*Note that the same amount of blood was injected into the cisterna of each dog. After the lapse of forty-eight hours, only 4.5 per cent or less of the red blood cells originally introduced into the cisterna could be recovered by complete subarachnoid drainage (lumbar laminectomy). After the first forty-eight hours practically all the erythrocytes had disappeared spontaneously (see Discussion in text).

water were withheld from the animals during the night preceding experimentation. A series of twenty adult dogs (without choice of breed or sex) was used for the experiments of which six were discarded for technical reasons. Each dog was anesthetized with sodium amytal intraperitoneally (50 mg. per kilogram of body weight) occasionally supplemented with one or two additional injections of 5 mg. per kilogram of body weight each. The same anesthesia was given for the ensuing laminectomy; a small amount of ether vapor (administered by cone) was necessary in a few dogs to insure proper depth of anesthesia. After anesthetization, a cisternal puncture was performed with a No. 20 gauge needle and the cisternal fluid was immediately examined to be certain there were no red cells present due to "needle trauma." Two cubic centimeters of whole blood were removed from a femoral artery and immediately injected into the cisterna magna through the indwelling needle which was then removed. At intervals varying from two and one-quarter hours to twenty-one days after the cisternal injection of blood (Table I), a laminectomy was performed and the tip of the caudal dural sac was doubly ligated with silk sutures and the roots of the cauda equina as well, quite beyond the extensions of the arachnoid around them, to insure the removal of all available fluid. The animal was then placed in the head-up position ( $80^{\circ}$  to  $85^{\circ}$ ) and a small glass tube, a few millimeters larger in bore than the diameter of the dural sac, was utilized for collection of the fluid. The ligated and free dural sac having been introduced into the glass tube, the dura was opened with forceps and scissors a few millimeters from the point of caudal ligation and all available spinal fluid collected by gravity. At the conclusion of the spontaneous flow of fluid from the dural sac, a few cubic centimeters of air were introduced through the small dural opening to displace any additional fluid in the ventricles or basilar cisternae (as in encephalography). Total amounts of fluid varying from 7 to 15 c.c. were thus obtained. The resultant fluid specimens were immediately examined for their individual erythrocyte content and the percentage of originally injected red blood cells recoverable after the various time intervals was computed.

*B. Clinical.*—Two patients with post-traumatic subarachnoid hemorrhage were studied with reference to the value of lumbar puncture in the removal of erythrocytes.

*CASE 1.*—E. W., a colored male, aged 30 years, was admitted to the University of Virginia Hospital (No. 137179) on Jan. 16, 1938, with a diagnosis of concussion and contusion of the brain associated with subarachnoid hemorrhage, following an automobile accident one and one-half hours before admission. Skull x-rays disclosed no fracture. As we were particularly interested at the time in the clinical evidence of disappearance of red blood cells from the spinal fluid in post-traumatic cases which might possibly be attributed to lumbar puncture, a series of five lumbar punc-

tures was done on the patient (Table II), the first one on the day after the injury and the last one nine days after the injury. He left the hospital thirteen days after admission and the injury (Jan. 29, 1938) was clinically well.

TABLE II

CASE I: E. W., AGED 30 YEARS (CEREBRAL CONCUSSION AND CONTUSION, JAN. 16, 1938)\*

DATE	INITIAL SPINAL FLUID PRESSURE (MM. OF WATER)	SPINAL FLUID REMOVED	R.B.C. PER CU.MM. IN SPINAL FLUID	PROTEIN
1/17/38†	200	8 c.c.	25,000	-----
1/19/38	130	8 c.c.	2,800	160 mg. %
1/21/38	185	8 c.c.	13,000	100 mg. %
1/23/38	290	4 c.c.	0	75 mg. %
1/25/38	60	5 c.c.	0	50 mg. %
(very slightly xanthochromic)				

\*Patient with post-traumatic subarachnoid hemorrhage. This case demonstrates the utility of lumbar puncture for the effective removal of red blood cells from the spinal fluid, as the great majority of the cells must have disappeared spontaneously (for explanation, see text).

†First lumbar puncture performed twenty-four hours after the hemorrhage.

CASE 2.—A. H., a white girl, aged 5 years, was admitted to the University of Virginia Hospital (No. 138430) on March 13, 1938, immediately after she had been struck by an automobile while walking on the road. She was semiconscious on admission, at which time the diagnosis was concussion and contusion of the brain with probable subarachnoid hemorrhage. For the next three days she remained semiconscious and weakness of the left side developed. Three days after the injury, three cranial burr openings were made to be certain that no massive subdural clot was developing; no such lesion was found but extensive bilateral contusion of the cerebral hemispheres with subarachnoid hemorrhage was demonstrated. She slowly improved and left the hospital thirteen days after the injury (March 26, 1938), at which time she was quite conscious and rational, a definite weakness of the left arm being the only neurologic abnormality. She has been seen in the out-patient department several times since discharge. When last examined, fifteen months after the injury (June 7, 1939), she was in excellent condition with no demonstrable weakness of any extremity.

TABLE III

CASE II: A. H., AGED 5 YEARS (BILATERAL CONTUSION OF THE BRAIN WITH SUBARACHNOID HEMORRHAGE, MARCH 13, 1938)\*

DATE	INITIAL SPINAL FLUID PRESSURE (MM. OF WATER)	SPINAL FLUID REMOVED	R.B.C. PER CU.MM. IN SPINAL FLUID	PROTEIN
3/14/38†	70	8 c.c.	70,000	240 mg. %
3/16/38	60	4 c.c.	40,000	60 mg. %
Bilateral superior temporal burr openings (3 in all) made immediately after second lumbar puncture (3/16/38), to rule out subdural bleeding; bilateral contusion of the brain and subarachnoid hemorrhage found				
3/18/38	50	4 c.c.	1,910	50 mg. %

\*Patient with post-traumatic subarachnoid hemorrhage. Note that even after three burr openings had been made in the skull, the dura opened and the right lateral ventricle punctured (March 16, 1938) in a patient with massive bilateral cerebral contusion and subarachnoid hemorrhage, it was found (two days after these procedures) that there was a marked reduction in red blood cell content of the spinal fluid (March 16, 1938, compared to March 18, 1938). (For explanation see text).

†First lumbar puncture performed twenty-four hours after the hemorrhage.

A series of three lumbar punctures (including the period before and after the burr openings) was performed on this patient (Table III).

One patient with spontaneous subarachnoid hemorrhage was also studied:

CASE 3.—P. R., a white male (University of Virginia Hospital No. 140192), aged 46 years, developed a spontaneous subarachnoid hemorrhage while driving his car on a long cross-country motor trip. On admission to the hospital (May 28, 1938) on the day of the hemorrhage, the patient was semiconscious and irrational. There was marked photophobia and cervical rigidity. A lumbar puncture was performed the day after admission (Table IV) and subsequently was repeated five times before the patient's discharge. He left the hospital clinically well eighteen days after admission and to the best of our knowledge has been in good health ever since, leading a sedentary life.

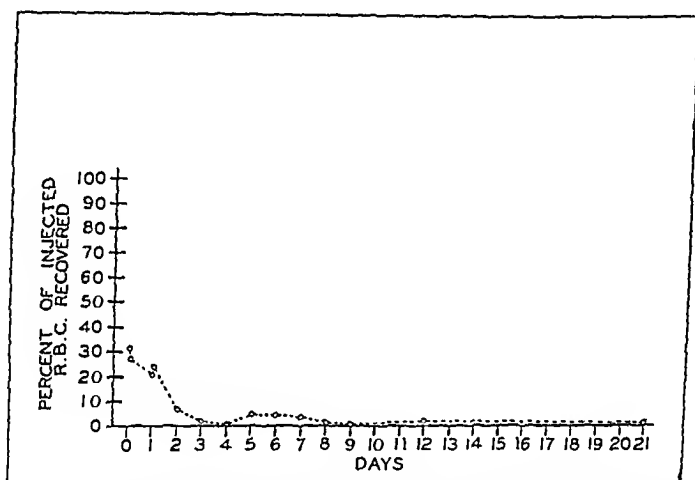


FIG. 1.—Composite curve showing the rate of cerebrospinal fluid clearance in a series of fourteen dogs in which all of the cerebrospinal fluid was withdrawn at various time intervals following the introduction of measured amounts of blood into the cisterna magna (subarachnoid space).

## RESULTS

A. *Experimental*.—The animal experiments confirm, in the main, Sprong's results (Table I and Fig. 1). Even following the removal of all available spinal fluid, it is demonstrated (Table I) that, after the first forty-eight-hour period following the injection of blood into the cisterna magna, there was never more than 4.5 per cent of the original number of erythrocytes recoverable and in most instances considerably less (1+ per cent or less). Even after such a short time interval as two and one-quarter hours, only 31.4 per cent of the erythrocytes originally introduced into the cisterna magna were recoverable by complete lumbar drainage. The curve in Fig. 1 shows the sharp drop in recoverable red blood cells after the second day following their introduction into the dog's cisterna magna. The remainder of the red blood cells must be accounted for by spontaneous disappearance, which fraction in the experiments carried out was never less than 95.5 per

cent after the first forty-eight hours. It should be emphasized that no spinal fluid was removed at any time, following the introduction of the blood into the cisterna magna, until the laminectomy was performed for the complete removal of the spinal fluid at periods varying from two and one-quarter hours to twenty-one days after the injection of blood.

B. *Clinical*.—An inspection of the data in Case 1 (Table II) shows that the lumbar punctures undoubtedly had little or nothing to do with the rapid disappearance of erythrocytes from the spinal fluid (see Discussion). One week after the injury (Jan. 23, 1938) no red blood cells were seen in the spinal fluid although only a total of 24 c.c. of fluid had been removed in the three previous punctures.

TABLE IV

CASE 3: P. R., AGED 46 YEARS (SPONTANEOUS SUBARACHNOID HEMORRHAGE, MAY 28, 1938)\*

DATE	INITIAL SPINAL FLUID PRESSURE (MM. OF WATER)	SPINAL FLUID REMOVED	R.B.C. PER CU.MM. IN SPINAL FLUID	PROTEIN
5/29/38†	70	7 c.c.	579,000	300 mg. %
5/31/38	120	5 c.c.	200,700	-----
6/ 2/38	210	15 c.c.	4,800	60 mg. %
6/ 5/38	90	5 c.c.	103	60 mg. %
6/ 8/38	98	6 c.c.	621	75 mg. %
6/11/38	115	6 c.c.	33	50 mg. %

\*Patient with spontaneous subarachnoid hemorrhage. Note that with the removal of only 12 c.c. of quite bloody spinal fluid (first and second lumbar punctures) the red blood cell content dropped to 4,800 per cu.mm. on the fifth day after the hemorrhage. Obviously, the removal of such a small amount of bloody fluid had little or nothing to do with such a great reduction; spontaneous disappearance must account for almost all of the erythrocytes (see Discussion in text).

†First lumbar puncture performed twenty-four hours after the hemorrhage.

In Case 2 (Table III) it is interesting to note that the third and final lumbar puncture was performed only two days after three burr openings of the skull had been made, with bilateral opening of the dura and tapping of a lateral ventricle. Even with this additional source of red blood cells in the cerebrospinal fluid, there was a marked reduction in erythrocyte content compared to the puncture performed immediately before the burr openings were made (1,910 R.B.C. per cubic millimeter compared with 40,000).

In Case 3 (Table IV), an instance of spontaneous subarachnoid hemorrhage, a lumbar puncture performed the day after admission showed 579,000 R.B.C. per cubic millimeter in the spinal fluid. Five subsequent punctures (the largest amount of fluid removed at any one time was 15 c.c.) in the ensuing thirteen days showed a rapid fall in red blood cell content (especially after the third day following the hemorrhage).

The data in Tables II, III, and IV clearly demonstrate that most of the erythrocytes in spontaneous or post-traumatic subarachnoid hemorrhage disappear spontaneously. Case 1 (Table II), an instance of post-

traumatic subarachnoid hemorrhage, may be used as an example, especially applicable for computation as the red blood cells had entirely disappeared from the spinal fluid by the seventh day (Jan. 23, 1938) after the injury. If one arbitrarily assumes that the total amount of cerebrospinal fluid present in this adult patient at any one time was 120 c.c., it is seen that on the day after injury there were  $3,000(\times 10^6)$  red blood cells in the spinal fluid ( $25,000 \times 1,000 \times 120$ ). The total number of red blood cells removed at the first puncture was  $200(\times 10^6)$ , at the second puncture  $20.4(\times 10^6)$  and at the third puncture  $104(\times 10^6)$ , making a total of  $324.4(\times 10^6)$  red blood cells removed in the first three lumbar punctures. Thus it is evident that the total number of erythrocytes removed by the three lumbar punctures compared to the total number present on the day after injury constituted only 10.8 per cent of the total ( $\frac{324.4}{3,000.0} = 10.8$  per cent). When it is recalled that the first computation of the total number of red blood cells in the cerebrospinal fluid in this patient (as in the other two clinical cases) was made twenty-four hours after the injury (during which interval innumerable red blood cells must have disappeared spontaneously), it is apparent that well over 90 per cent of the erythrocytes must have disappeared spontaneously in this patient (Case 1) within one week (Jan. 23, 1938) of the injury, if not before.

Considering the case of spontaneous subarachnoid hemorrhage (Case 3, Table IV), the results are even more striking. On the basis of the red blood cell count in the spinal fluid on the day after the hemorrhage (579,000 per cubic millimeter) there were  $69,480(\times 10^6)$  red blood cells present, if one allow 120 c.c. as the total amount of cerebrospinal fluid present, an average figure for an adult patient. Six lumbar punctures were carried out on the patient; the total number of red blood cells removed in the six punctures was calculated as  $5,133.4(\times 10^6)$ . It is seen, therefore, that the total number of erythrocytes removed by all the punctures, compared to the total number present on the day after the hemorrhage, constituted but 7.4 per cent of the total ( $\frac{5,133.4}{69,480} = 7.4$  per cent), so that 92.6 per cent of the red blood cells must have disappeared spontaneously after the first twenty-four hours following the hemorrhage, in addition to the red blood cells that were undoubtedly hemolyzed or otherwise eliminated from free circulation in the cerebrospinal fluid during the first twenty-four hours following the intracranial vascular accident, during which latter period no lumbar puncture was performed.

#### DISCUSSION

The experimental work is more analogous to spontaneous subarachnoid hemorrhage than it is to the post-traumatic variety, as no parenchymatous brain injury was induced.

It is demonstrated that, following the first forty-eight hours after the introduction of a measured amount of blood into the dog's cisterna magna, only 4.5 per cent or less of the erythrocytes introduced could be recovered by complete subarachnoid drainage (lumbar laminectomy). After the first forty-eight hours, nearly all the red blood cells had disappeared spontaneously. The slightly greater number of erythrocytes recoverable in Dogs 8, 9, and 10 (Table I) than in Dogs 6 and 7 may be explained on the basis of possible continued oozing (as in clinical cases) in the former dogs. Even with this possibility, it is apparent that the average lumbar puncture, as performed clinically, removes few red blood cells, relatively or absolutely. Thus these experiments substantiate the opinion that, so far as removal of erythrocytes is concerned, lumbar puncture is of slight value, as spontaneous disappearance undoubtedly eliminates most of the red blood cells, especially after the first forty-eight hours.

The experiments described above were not devised nor were they expected to explain by what process or processes the erythrocytes disappeared from the subarachnoid space, but they do demonstrate the relative futility of lumbar puncture for their removal. The red blood cells are not entirely eliminated by hemolysis, although this is perhaps the most important process accounting for their disappearance. It must be recalled, however, that Essick<sup>1</sup> in 1920 demonstrated that arachnoid cells are capable under certain conditions of becoming phagocytes and Bagley<sup>14</sup> has clearly shown in the experimental animal that, when blood is introduced into the subarachnoid space, certain of the arachnoid (phagocytic) cells become filled with blood pigment resulting from the engulfment of erythrocytes. He also showed that the pigment-laden cells are found even in the chronic stage of meningeal thickening secondary to the injection of blood into the cisterna magna or elsewhere in the subarachnoid space. Furthermore, all surgeons and pathologists who have seen considerable numbers of brains that had been subjected to trauma or following spontaneous subarachnoid hemorrhage are familiar with the fact that blood becomes agglutinated in the subarachnoid spaces over the cerebral convexities and in the basilar cisternae with great frequency; by this sequel to subarachnoid hemorrhage still more erythrocytes become enmeshed and are incapable of removal by lumbar puncture. It is probable that these three processes: (a) hemolysis, (b) phagocytosis by arachnoid cells, and (c) enmeshment and agglutination of intact erythrocytes in the subarachnoid space account for the major portion, if not the entire number, of red blood cells that disappear spontaneously from the cerebrospinal fluid after subarachnoid hemorrhage.

A plea is made for reduction of the frequency of lumbar puncture in cases of subarachnoid bleeding. At the present time in this clinic such punctures are infrequently performed in post-traumatic and in

spontaneous subarachnoid hemorrhage. In a previous communication from this clinic<sup>15</sup> it was reported (1938) that lumbar puncture was performed in only 15 per cent of all head injury cases. This has been confirmed by a more recent analysis (1940) of 391 additional cases (consecutive admissions) of all types of head injury in which lumbar puncture was performed in 15.3 per cent of all cases.<sup>16</sup> Dandy<sup>17</sup> considers it of little or no use in any post-traumatic case.

It is still rather widely believed that lumbar puncture should be frequently performed in cases of spontaneous and post-traumatic subarachnoid hemorrhage. This is apparent from a review of the literature of the last few years in regard to spontaneous subarachnoid hemorrhage alone. To refer to only a few of the many recent writers on this subject: Leary and Myerson<sup>18</sup> in 1931; Blackford,<sup>19</sup> Strauss, Globus, and Ginsburg,<sup>20</sup> and Ohler and Hurwitz<sup>21</sup> in 1932; Hyland<sup>22</sup> and Osterman<sup>23</sup> in 1933; and Eley<sup>24</sup> and Waite<sup>25</sup> in 1934; all recommended lumbar punctures with removal of rather large amounts of spinal fluid until it becomes clear. Many other writers could be quoted with similar views. Also, the same viewpoint is widespread among the profession in regard to post-traumatic subarachnoid hemorrhage.

It appears that these views are, for the most part, without sound physiologic or pathologic foundation for reasons previously stated. They are certainly not borne out by the experimental data (reported herewith) having to do with the spontaneous disappearance of red blood cells from the spinal fluid. We are inclined to agree with the opinion of Hall,<sup>26</sup> who, in discussing spontaneous subarachnoid hemorrhage, prefers lumbar puncture initially for diagnosis and subsequently only to relieve signs of medullary compression such as respiratory distress, bradycardia, and stupor, for which purpose it is probably justified. The same statement holds true for occasional post-traumatic cases in which one is certain that there is no massive sub- or extradural clot, either from the clinical signs or by previous operation.

#### CONCLUSIONS

1. Experimental and clinical evidence is presented to demonstrate that lumbar puncture, when used for the removal of red blood cells from the subarachnoid space, is almost completely ineffective.

2. This fact, not generally known and accepted, should be more universally applied to clinical cases; i.e., lumbar punctures should not be done for the sole purpose of removing erythrocytes from the subarachnoid space.

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## ABSORPTION OF SULFANILAMIDE FROM BURNED SURFACES

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THE tendency of burns to become infected with streptococci<sup>1</sup> and the success which has attended the use of sulfanilamide locally in compound fractures<sup>2</sup> and other forms of trauma caused us to make these observations on the effect of sprinkling the dry powder on small areas in eight cases of burns. The rapidity of absorption and the high blood levels obtained in several cases were so striking that we are making this report to call attention to the probable value of this method of administering sulfanilamide prophylactically and therapeutically, and incidentally to add evidence in the debated question of whether or not there is considerable absorption of diffusible material from burned skin.

The work of Underhill, Kapsinow, and Fisk<sup>3</sup> has often been cited as opposing the so-called toxic theory of the cause of death from burns. They showed that when phenolsulphonephthalein or strychnine was injected into burned areas, its absorption was distinctly inhibited. One might infer, therefore, that it is unlikely that any hypothetical toxic substance would be taken up by the blood stream and distributed to other parts of the body.

Mason, Paxton, and Shoemaker<sup>4</sup> found that potassium iodide was readily absorbed from burned areas. Mitchiner<sup>5</sup> states that Petit and Lister employed perchloride of mercury in the treatment of burns in the nineteenth century, with the idea of precipitating the surface proteins. It is said that all of the patients so treated died or suffered severely from mercurial poisoning. Recently, Arnaud<sup>6</sup> reported his experience with the treatment of nine cases of burns with mercurochrome dressings. Nephritis and other symptoms of mercurial poisoning developed, and mercury was detected in the urine in twenty-four hours. In a comment on this article, Graham<sup>7</sup> aptly warns against any further use of mercurochrome in the treatment of burns. To these instances of active absorption from burned surfaces, we add the following data with regard to sulfanilamide.

### CASE REPORTS

CASE 1.—M. W., a 24-year-old white woman, suffered second degree burns of the arms and face in a blowtorch explosion. Two hours after the injury, sulfanilamide powder was applied to the extensor surface of the left forearm, the area measuring

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Fig. 1.—Showing sulfanilamide powder applied to the forearm of patient in Case 1. The photograph was taken two and one-half days after the initial application. The ruler parallel to the forearm is in centimeters.

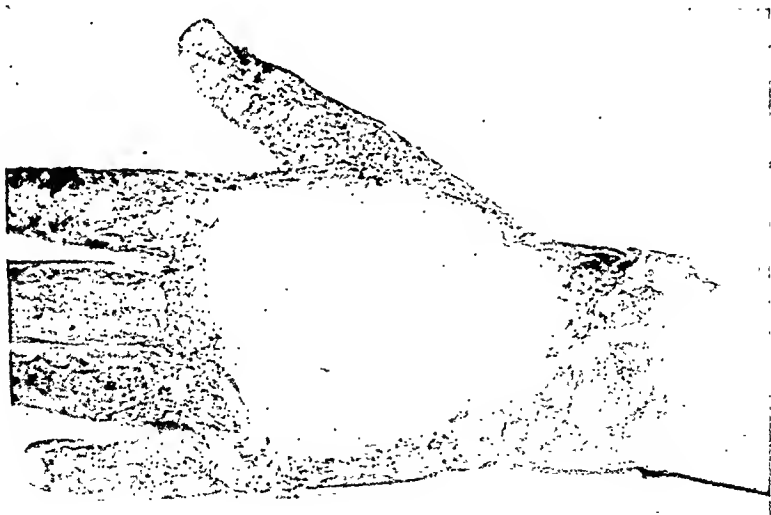


Fig. 2.—Showing sulfanilamide powder applied to the hand of patient in Case 2. The photograph was taken two and one-half days after the initial application. The ruler parallel to the hand is in centimeters.

15 cm. by 4 cm. (Fig. 1). Approximately 5 Gm. of powder was applied initially, and small amounts were sprinkled on at intervals thereafter, making a total of about 40 Gm. being applied over a period of three and one-half days. The curve of the blood sulfanilamide level is shown in Fig. 3. A level of 9.4 mg. was obtained. No infection developed in this area or in the other areas which had been treated with tannic acid jelly.<sup>8</sup>

CASE 2.—D. W., a 29-year-old white man, received burns of the hands and face in the same explosion in which the patient in Case 1 was burned. Two hours after the accident, sulfanilamide powder was applied to an area measuring 8 cm. by 6 cm. on the back of the left hand (Fig. 2), approximately 30 Gm. of powder being used altogether. A blood level of 7.8 mg. was reached on the third day. Healing was rapid and uneventful.

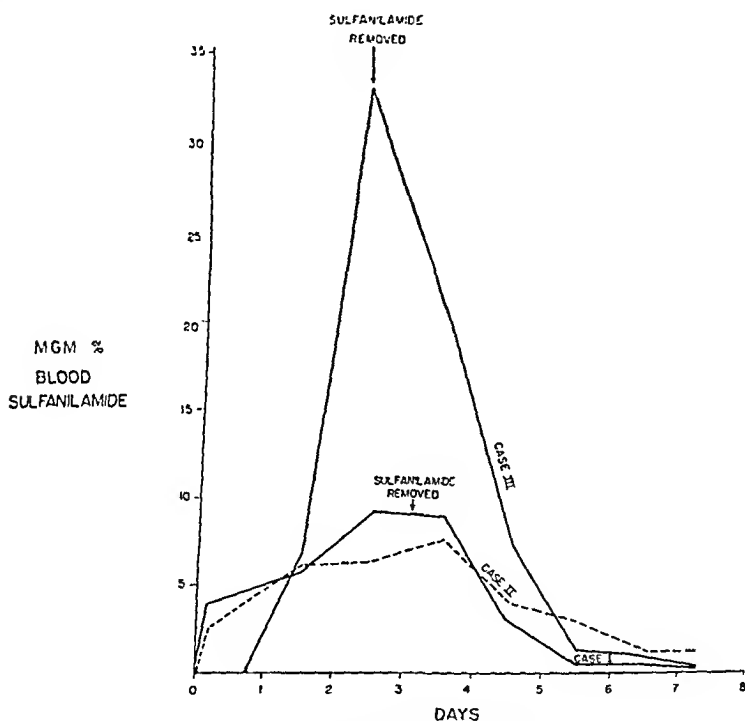


Fig. 3.—Curves showing the rate of absorption of sulfanilamide from the burned areas in Cases 1, 2, and 3.

CASE 3.—M. K., a 38-year-old white man, sustained a third degree burn of the left leg in a gasoline fire. Primary treatment was with tannic acid jelly. Infection developed under the eschar, and it was removed; cultures showed *Bact. pyocyaneus* and nonhemolytic streptococci. Sulfanilamide powder was sprinkled on the leg over an estimated area of nearly 30 by 60 cm. Approximately 60 Gm. of the powder was used altogether. The next morning the patient was put in a tub bath, and afterward more powder was put on. He became cyanotic and confused. The blood sulfanilamide level was 33 mg. The remainder of the powder on the leg was removed by irrigation. Treatment of the infected granulating surface was continued with daily brine baths, and split grafts were applied early.

Isolated observations were made on five additional cases (Table I).

TABLE I

CASE NO.	SIZE OF AREA	LEVEL OF BLOOD SULFANILAMIDE	NO. DAYS INTER- VENING
4	4 by 5 cm.	2.3 mg.	4
5	5 by 6 cm.	4.5 mg.	3
6	3 by 4 cm.	1.0 mg.	6
7	4 by 5 cm.	1.2 mg.	5
8	6 by 3 cm.	2.0 mg.	2

## DISCUSSION AND CONCLUSIONS

In presenting this report, it is not our intention to advise the widespread use of sulfanilamide powder in the treatment of burns. In fact, our experience with putting the powder on very small areas indicates that there is danger of overdosage if the drug is used indiscriminately on larger areas. It would appear to be a useful procedure in the case of a large infected burn to put the powder on a small portion and to obtain the desired blood level by this route rather than by giving the drug by mouth. Nausea and vomiting are common enough in burns without the additional factor of chemotherapy by mouth. It is possible that further experience will produce a technique whereby the drug can be used routinely in a prophylactic manner to prevent secondary streptococcal infection.

This experience is additional evidence against the view that burned tissues form a poor absorbing surface.

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# PEPTIC ULCER AND DIARRHEA FOLLOWING THE REMOVAL OF THE PREVERTEBRAL GANGLIA IN DOGS

## THE ANTISPASMODIC EFFECTS OF MAGNESIUM SULFATE, PENTOBARBITAL, AND ATROPINE SULFATE

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THE close association of psychic disturbances and diarrhea is well known to the clinician. Although the mechanism involved is not understood, there is experimental evidence which points to a sympathetic-parasympathetic imbalance as a very important factor. Popielski<sup>1</sup> reported his experience with removal of the celiac and superior mesenteric ganglia in twenty-two dogs. After operation all of the animals developed watery diarrhea and passed both mucus and bright red blood in the stools. Two animals died nine and twenty-five days after gangliectomy from the inanition attending the severe diarrhea. In the animals that survived over a two-week period, it was usually found that the blood and mucus disappeared from the stools and diarrhea alternated with formed feces. Complete protocols were given for the autopsy of five animals and in all of these ulcers were found in the stomach and duodenum. Other changes noted were marked hyperemia and hemorrhagic erosions along the gastrointestinal tract.

Laignel-Lavastine<sup>2</sup> wrote a comprehensive review of the celiac plexus and its function. He concluded from his experiments on complete removal that this plexus exerts a restraining action on the movements of the intestine, hence the bloody dejecta and diarrhea which are noted after ablation.

Vedova<sup>3</sup> removed the right and left celiac ganglia in dogs and also injected alcohol into the plexus. No mention is made of diarrhea after such procedures. Donati<sup>4</sup> removed only the left celiac ganglion in dogs without a disturbance of bowel activity. Grundelfinger<sup>5</sup> excised both celiac ganglia and does not report any disturbance in the frequency of bowel movements. The absence of diarrhea in these experiments may well be due to the incomplete removal of the prevertebral ganglia, for in the experiments of Popielski and Laignel-Lavastine the superior mesenteric ganglia were also excised. Donati<sup>4</sup> and Peiper<sup>6</sup> make no reference to diarrhea after the removal of the celiac plexus in rabbits.

The implications of the findings by Popielski and Laignel-Lavastine are of sufficient importance to reconsider carefully. They suggest that

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in dogs a radical removal of the celiac plexus will effect a marked diarrhea. In addition to repeating their work, the present experiments include a study of the effect of this operation upon rectal tonus and motility. The influence of certain drugs on the increased rectal contractions was tested after ganglionectomy. The operative procedure used by other investigators was enlarged to include removal of the inferior mesenteric ganglion, which lies quite apart from the celiac plexus. *Subsequently in this paper, the term prevertebral ganglionectomy will be used to denote the removal of the right and left celiac ganglia, the superior and inferior mesenteric ganglia.*

#### METHODS

Male and female dogs of medium size were used. They were fed on a diet of boiled meat and pasteurized milk throughout the experiment. During the three days preceding the operation, the stools were examined carefully for gross evidence of blood and mucus.

Studies were made of rectal contractions in all of the animals at two- or three-day intervals before and after operation. For this purpose a small balloon attached to a catheter was inserted by means of a forceps through a proctoscope in the rectum. The balloon was placed two inches above the anus and the proctoscope withdrawn. After connecting the balloon to a mercury manometer, 40 c.c. of air were introduced slowly through a sidearm in the system. A record of the contractions was made over a period of fifteen to twenty minutes with a writing arm recording the oscillation of the mercury on a smoked drum. In each study a record was made of the pressure within the balloon when it was filled with 40 c.c. of air, outside the animal (Fig. 1).

After it had been established that increased rectal contractions were present after prevertebral ganglionectomy, the influence of intravenous pentobarbital,  $MgSO_4$ , or atropine sulfate was tested in various animals. Throughout the work with the balloon, no difficulty was encountered in obtaining records which were free from the elevation which occurs when the animals move or strain.

For the operative procedure ether anesthesia and sterile technique were used. Through a midline abdominal incision the inferior mesenteric, superior mesenteric, and celiac ganglia were removed. In all of the animals the celiac, superior, and inferior mesenteric arteries were cleaned of nerve tissue for a distance of 2 cm.

A preliminary control operation was performed ten days before removal of the ganglia in two animals. The abdomen was opened and retraction of the intestines was maintained for one hour so that all of the trauma except the actual excision of the nerves was duplicated. The animals were subsequently studied with the rectal balloon and one week later were subjected to ganglionectomy.

In two other animals the abdomen was opened under ether and the intestines retracted as for ganglionectomy over a one-hour period. One

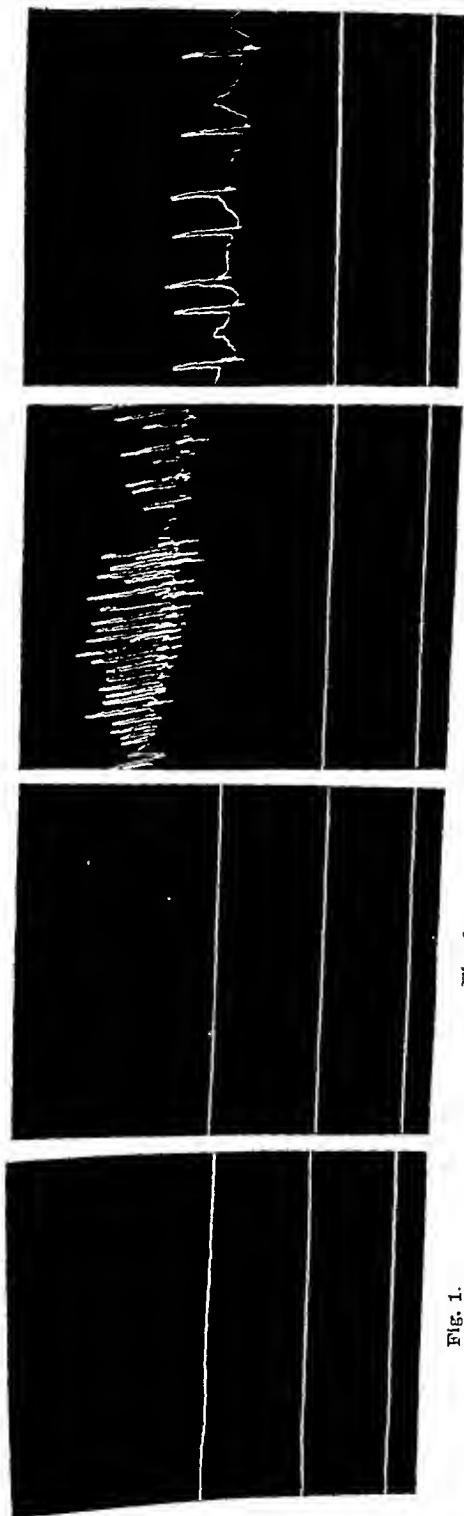


Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Figs. 1-4.—Rectal contractions from Animal 8. They show that simple laparotomy with retraction of the intestines is not responsible for the increased contractions. Subsequent ganglionectomy, in such an animal elicits the increment in rectal activity as noted in all nine animals examined. Each figure represents a three-minute period. The upper line is the balloon in the rectum. The lowest line is the base; the middle line is the balloon containing 40 c.c. of air outside the animal; animal 8, before operation; Fig. 2, one week after simple laparotomy; Fig. 3, day after prevertebral ganglionectomy; Fig. 4, one week after prevertebral ganglionectomy.

week later they were sacrificed for examination of the gastrointestinal tract. In sacrificing animals, they were first etherized, the abdomen was opened, and the entire gastrointestinal canal excised and opened. The whole specimen was preserved in 10 per cent formalin and at a later date microscopic slides were prepared of the abnormal areas. These were stained with hematoxylin and eosin.

### RESULTS

In all but two of the animals, formed stools were passed during the three days before operation. These two had mushy, unformed stools, which was attributed to the use of horse meat in their diet. No animal in this series showed gross blood or mucus in the stools preoperatively. All four dogs subjected to simple laparotomy had formed stools after this operation.

The studies with the balloon before operation showed uniform results in all animals. Figs. 1 and 5 are typical curves.

Table I gives the survival period and autopsy findings in the nine animals subjected to ganglionectomy. Animals 1 and 2 survived less than four days. One of these animals suffered peritonitis in the left upper quadrant of the abdomen from a perforated gastric ulcer; the other had an intussusception of the terminal ileum through the ileocecal valve with gangrene and peritonitis.

Animals 3 and 4 were sacrificed at a time when they could only survive a period of hours, to judge by their weakened condition. They suffered severe weight loss despite a good appetite and lost so much strength that they could not eat or even stand up toward the end. The diarrhea in these animals was so acute that they soiled themselves badly and had ulcers and erosions of the skin where the digestive juices had been deposited.

The remaining animals withstood the operation quite well and might have survived indefinitely had they not been sacrificed for examination of the gastrointestinal tract.

In all nine animals subjected to ganglionectomy the following results were observed:

1. *Diarrhea*.—This became evident as soon as the animals regained consciousness. The discharge consisted of mahogany colored liquid with large amounts of mucus. When the animals commenced to eat, undigested food would appear in the feces. Animal 4 drank some milk forty-eight hours after operation, and in fifteen minutes passed bile-stained milk curds by anus. Characteristic of the feces was a powerful stench, as has also been noted by other investigators. The diarrhea was most pronounced during the first ten days after operation. If the animals were able to survive this time in a fair state of nutrition, the diarrhea lessened and the undigested meat particles disappeared from the feces. The stools were unformed in all but one of the surviving

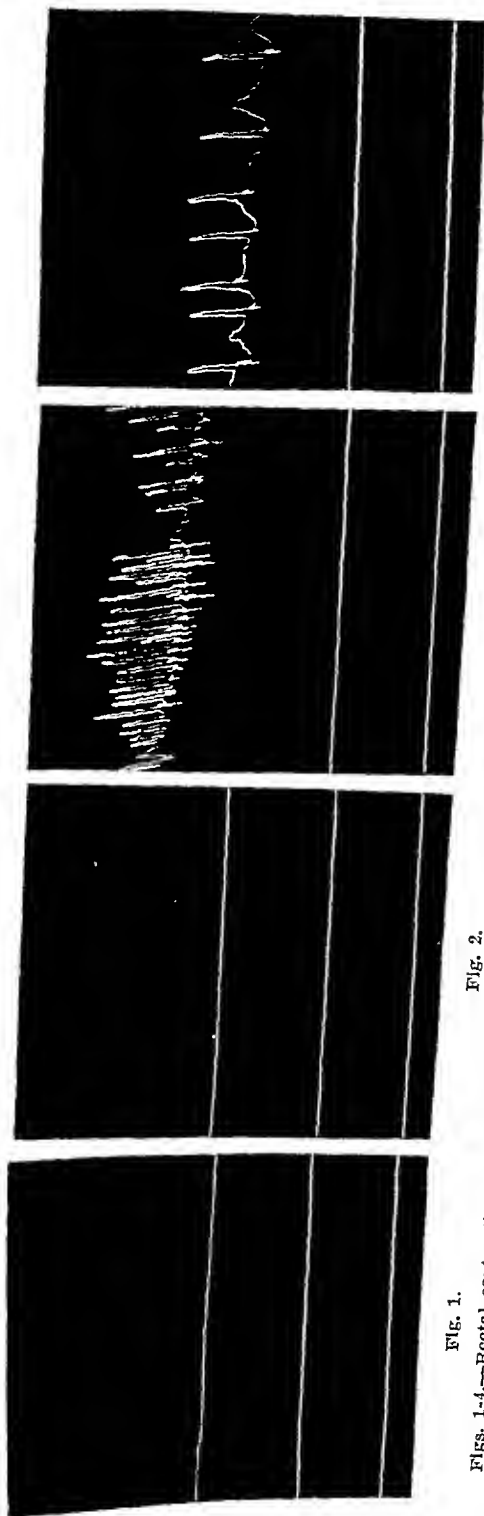


Fig. 1.

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Figs. 1-4.—Rectal contractions from Animal 8. They show that simple laparotomy with retraction of the intestines is not responsible for the increased contractions. Subsequent ganglionectomy in such an animal elicits the increment in rectal activity as noted in all nine animals examined. Each figure represents a three-minute period. The upper line is the balloon in the rectum. The middle line is the base; the lowest line is the rectum. Recording is by mercury manometer, and pressure exerted is twice the height of the record. Fig. 1, Animal 8, before operation; Fig. 2, one week after simple laparotomy; Fig. 3, day after prevertebral ganglionectomy; Fig. 4, one week after prevertebral ganglionectomy.

TABLE I—CONT'D

ANIMAL	POST- OPERA- TIVE DAY OF DEATH	CAUSE OF DEATH	CONDITION AT DEATH	FINDINGS AT AUTOPSY
6.	24	Killed under ether	Good health; holding weight; two or three watery stools a day	Edema of entire gut; nothing abnormal either grossly or microscopically save for edema
7.	7	Killed under ether	Watery stools with mucus and flecks of red blood; undigested food in feces	Edema of entire gut; three (0.5 by 0.3 cm.) ulcers of lesser curvature; 0.3 cm. wide ulcer crater in fundus with rugae converging on it; 5 by 2 cm. area of ulceration and erosion along greater curvature; intramucosal hemorrhages of ileocecal valve; section of gastric ulcers showed destruction of muscularis mucosa with atypical epithelium at edge of ulcer; considerable scar tissue in base of ulcer
8.	7		Watery stools with mucus and flecks of red blood; undigested food in feces	Entire gut edematous; intramucosal hemorrhages on tips of rugae in cecum; intramucosal hemorrhages of ileocecal valve
9.	10		Loose, watery stools, four to six daily	Gastric ulcer, 1 cm. wide, over middle of greater curvature of stomach; 0.5 cm. wide ulcer with red edges 15 cm. above ileocecal valve; this was almost perforated; intramucosal hemorrhages of ileocecal valve; hyperemia of colon, most marked in cecum, with some intermucosal hemorrhages microscopically

animals during the period of observation. The exception, Animal 5, had three or four mushy stools a day alternating with formed stools two months after ganglionectomy. Animal 6 continued to have watery feces with mucus twenty-four days after operation.

2. *Mucus*.—Gross amounts of mucus are not normally present in dog's feces, but, after removing the celiac, superior and inferior mesenteric ganglia, large particles of mucus were present in each defecation. At times long strips of mucus were passed, and these appeared to be casts of the colon. The amount of mucus diminished as the diarrhea subsided.

3. *Bloody Stools*.—All animals passed blood in the feces after ganglionectomy. In three of the dogs this amounted to 1 dr. or more on several occasions, but in the others only blood-stained mucus was passed.

TABLE I

SUMMARY OF PATHOLOGIC FINDINGS IN 9 DOGS SUBJECTED TO CELIAC GANGLIONECTOMY

ANIMAL	POST- OPERA- TIVE DAY OF DEATH	CAUSE OF DEATH	CONDITION AT DEATH	FINDINGS AT AUTOPSY
1.	3	Peritonitis	Severe diar- rhea; blood in stools	Peritonitis localized to left upper quadrant; perforated ulcer on greater curvature of stomach; three ulcers (0.4 to 0.8 cm. wide) on the lesser curvature; dark blood throughout the entire gut and marked hyperemia of mucosa
2.	3	Peritonitis	Severe diar- rhea; blood in stools	Intussusception of terminal 20 cm. of ileum through ileocecal valve with gangrene of terminal ileum and peritonitis; stomach spastic with multiple intramucosal hemorrhages and erosions; these changes most marked on tips of rugae; marked duodenitis and hyperemia of entire gut
3.	14	Too weak to eat; killed under ether	Marked loss of weight; severe diarrhea; multiple ulcers of skin where feces had touched	Marked edema of entire gut; two ulcers over pyloric ring (0.4 by 0.2 cm. and 0.3 by 0.1 cm.) with red edges; intramucosal hemorrhages in cecum running at tips of rugae in a transverse linear pattern; pyloric ulcers, on section, invaded the muscularis mucosa
4.	12	Too weak to eat; killed under ether	Same as Animal 3	Edema of entire gut; marked duodenitis both grossly and microscopically; two superficial erosions 0.6 cm. wide at junction of ileum and jejunum; lower half of colon showed marked hyperemia; intramucosal hemorrhages of ileocecal valve
5.	2 mo.	Killed under ether	Good health; formed stools alternating with mushy; all stools tarry black	Marked edema of entire gut; at junction of jejunum and ileum was a 1 by 0.8 cm. firm, white scar extending through entire wall of gut; sections showed muscle occupied largely by fibrous tissue and a thin layer of epithelium without villi; for 30 cm. below this scar the mucous membrane was markedly hyperemic both grossly and microscopically; lumen of gut contained old blood and on section many intramucosal hemorrhages were seen

Tenesmus and straining were invariably associated with the appearance of blood. The animal would defecate watery feces after which it continued to strain for several minutes. Thick mucus was then expressed followed by blood-tinged mucus. If the tenesmus continued even longer, a drop or two of bright red blood would be passed. The blood disappeared as the diarrhea subsided. It is assumed that the blood passed at the end of defecation came from the lower gut. Whether changed blood from higher up in the intestinal canal was also present in the feces cannot be stated with certainty. Suggestive evidence in favor of this was furnished by Animal 5. Over a two-month period this animal passed black stools when other animals in the colony had dark brown stools on the same diet. At autopsy a 30 cm. segment of ileum was found to be markedly inflamed and to contain bloody fluid. Microscopic section of this area showed widely dilated blood vessels in the villi and intramucosal hemorrhages.

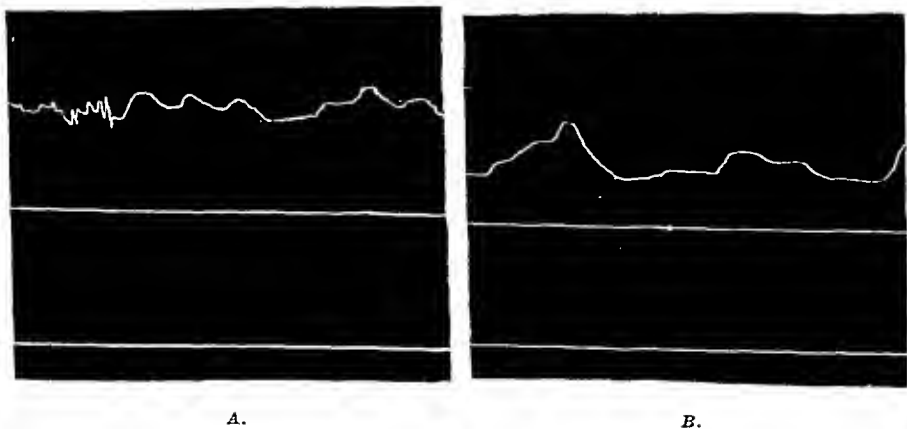


Fig. 9.—The increased rectal contractions are still present as long as twenty-four days and two months after prevertebral ganglionectomy. *A*, Animal 6, rectal contractions twenty-four days after ganglionectomy; *B*, Animal 5, rectal contractions two months after ganglionectomy.

4. *Increased Rectal Contractions.*—All nine animals subjected to ganglionectomy were studied with the balloon catheter before and after operation. There were none or only occasional slight contractions before operation (Figs. 1 and 5). Whereas there were individual differences, all animals showed increased rectal activity after ganglionectomy. In most animals this was greatest on the first few days after operation, and the balloon was often defecated soon after insertion. In the two that succumbed from the effects of the severe diarrhea there was a gradual increase in response with the maximum reached just before death (Figs. 5-8). In no animal studied did the rectal response return to the normal preoperative level. One animal was studied two months and another twenty-four days after operation (Fig. 9 *A* and *B*). In the four control animals there was no essential difference between the preoperative

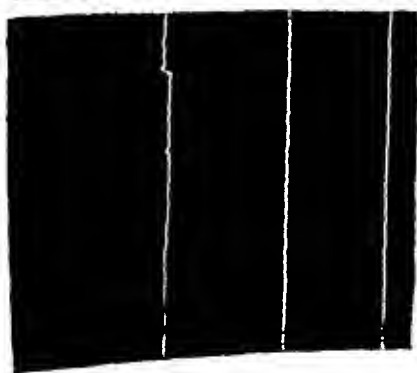


Fig. 5.



Fig. 6.

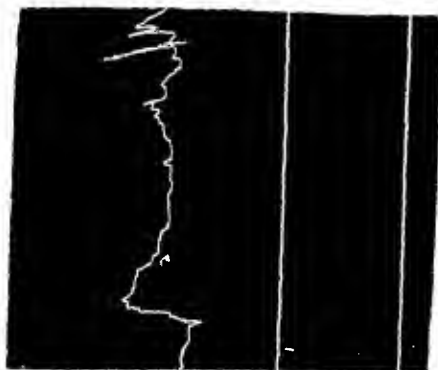


Fig. 7.

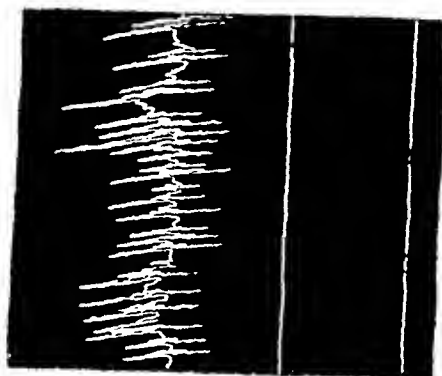


Fig. 8.

Figs. 5-8.—From Animal 4 which succumbed from the severe diarrhea following prevertebral ganglionectomy. Note the increase in rectal activity with time. Each figure is a three-minute interval of rectal contractions. Fig. 5, Animal 4, preoperatively; Fig. 6, nine days after operation; Fig. 7, five days after operation; Fig. 8, eighteen hours after operation.

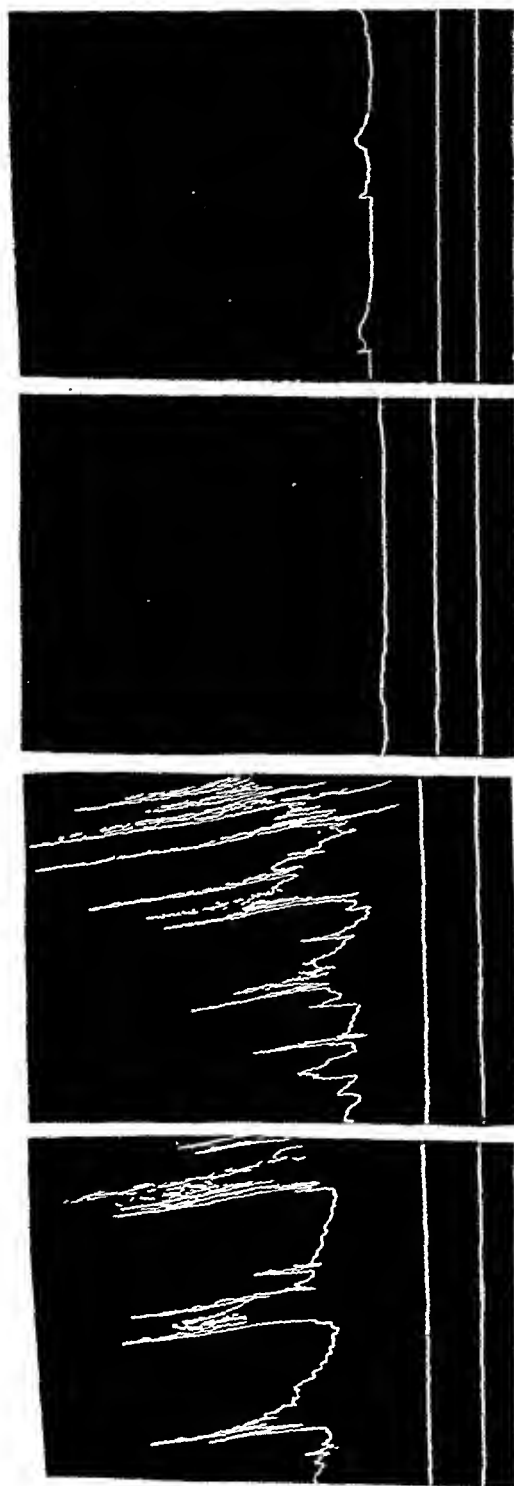


FIG. 10.

FIG. 11.

FIG. 12.

FIG. 13.

*Figs. 10-13.*—The effect of intravenous calcium gluconate and magnesium sulfate on the rectal contractions after prevertebral ganglionectomy. Calcium gluconate has no effect when given in relatively small doses. Twenty-five per cent magnesium sulfate abolishes the rectal contractions for long periods. The control observations in the two experiments were essentially the same. Calcium gluconate was given on the sixth and magnesium sulfate on the seventh postoperative day. FIG. 10, Control; FIG. 11, immediately after 5 c.c. of 10 per cent calcium gluconate intravenously; FIG. 12, immediately after 5 c.c. of 25 per cent  $M_2SO_4$  intravenously; FIG. 13, one and three-fourths hours after recording shown in FIG. 13.

studies with the balloon and those after simple laparotomy. The two control animals subjected to ganglionectomy had the same increase in rectal contractions as the other dogs. (Figs. 1-4.)

During the preoperative period two of the animals had a watery diarrhea caused by the eating of some horse meat. Rectal irritability was studied during this period and showed no essential difference in the curves from the normal.

*Necropsy Findings.*—Table I gives in summary form the findings at autopsy. Satisfactory microscopic studies were not available in Animals 1 and 2 which died during the night. These animals were the only ones to show marked hyperemia of the entire gut grossly. In the others the hyperemia was localized. Four of the nine animals showed peptic ulcers. Two of these had discrete ulcers on both greater and lesser gastric curvatures (Animals 1 and 7). Animal 7 had also a 5 by 2 cm. area of irregular ulceration along the greater curvature and an acute ulcer in the lower ileum which had almost perforated. Animal 9 had a 1 cm. wide ulcer on the greater curvature toward which the rugae converged. Animal 3 showed two acute ulcers directly overlying the pylorus. On microscopic study of the lesions in Animals 3, 7 and 9, the ulcers were found to extend beneath the muscularis mucosa. There was an acute inflammatory reaction throughout the base and at the edges atypical epithelium was found and regeneration appeared to be in progress.

Animal 2 had a marked gastritis with intramucosal hemorrhages along the tips of the rugae, and Animal 4 showed a severe duodenitis. Animal 5, which was sacrificed two months after ganglionectomy, had a white scar at the junction of the ileum which was covered with a thin layer of epithelium without villi. Five animals showed gross interstitial hemorrhages in the mucosa overlying the ileocecal valve. There were no ulcerations or gross erosions observed in the colon, but hyperemia was noted grossly in five animals. The microscopic sections taken from the areas of hyperemia and intramucosal hemorrhage in these animals showed a wide dilatation of capillaries. In small foci, at the superficial border of the mucosa, there appeared hemorrhagic areas which had caused a necrosis of the surrounding tissue and of the overlying epithelium. In other areas there were seen large round cells loaded with hemosiderin where earlier subsurface hemorrhages might well have occurred.

In the two animals subjected to simple laparotomy, no demonstrable abnormalities of the gastrointestinal tract were found.

*Inhibition of Rectal Contractions With Drugs.*—The animal with its celiac, superior and inferior mesenteric ganglia removed constitutes an excellent test object for antispasmodic agents. Only  $MgSO_4$ , pentobarbital, and atropine were tested in these animals. They were all given intravenously in large amounts. Atropine sulfate (0.5 mg.) was tested on two,  $MgSO_4$  (5 c.c. of 12.5 or 25 per cent solution) on four, and pentobarbital (anesthetic dose) on two animals. In each instance there was

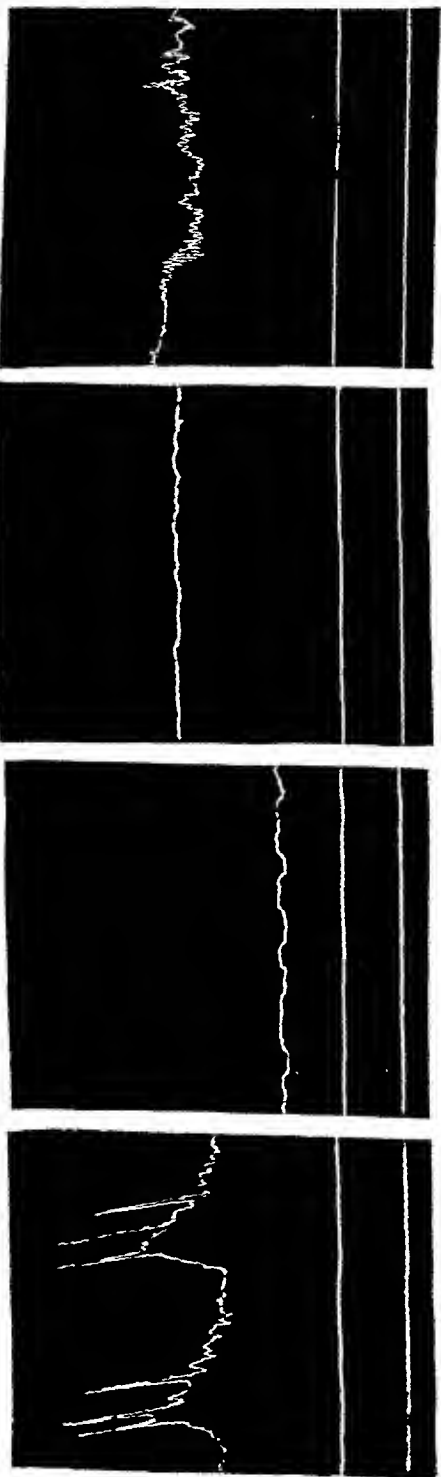


Fig. 17.

Fig. 18.

Fig. 19.

Fig. 20.

Figs. 17-20.—The effect of an anesthetic dose of nembutal on the rectal contractions of Dog 5, four days after prevertebral ganglionectomy. All are three-minute intervals and show the prolonged inhibiting effect. Further observations were impossible because the animal was too restless during the early recovery period. Fig. 17, Control; Fig. 18, immediately after anesthetic dose of nembutal intravenously; Fig. 19, one hour after tracing shown in Fig. 18; Fig. 20, two and three-fourths hours after tracing shown in Fig. 18.

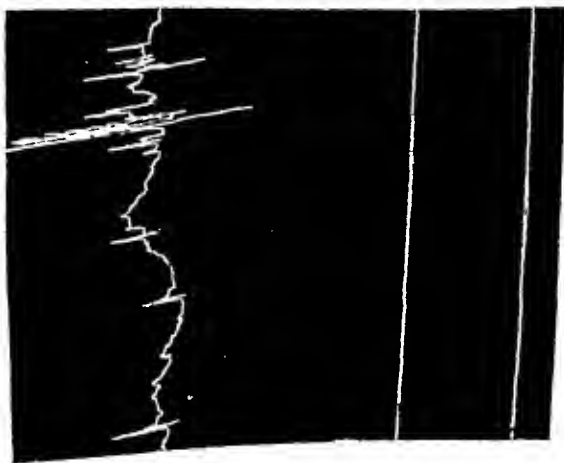


Fig. 14.

Figs. 14-16—The effect of intravenous atropine on rectal contractions in Animal 3, six days after prevertebral ganglionectomy. The time intervals are three minutes. Whereas atropine abolishes contractions, it does so only for a short time as compared with magnesium sulfate. Fig. 14, Control in Animal 3, six days after ganglionectomy; Fig. 15, immediately after atropine sulfate, 0.5 mg. intravenously; Fig. 16, one hour after tracing shown in Fig. 15.

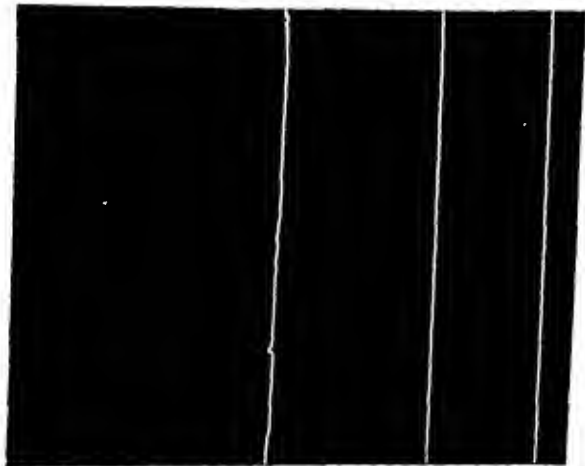


Fig. 15.

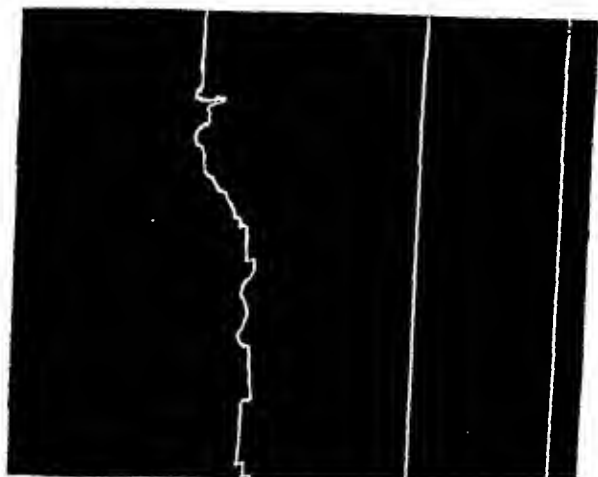


Fig. 16.

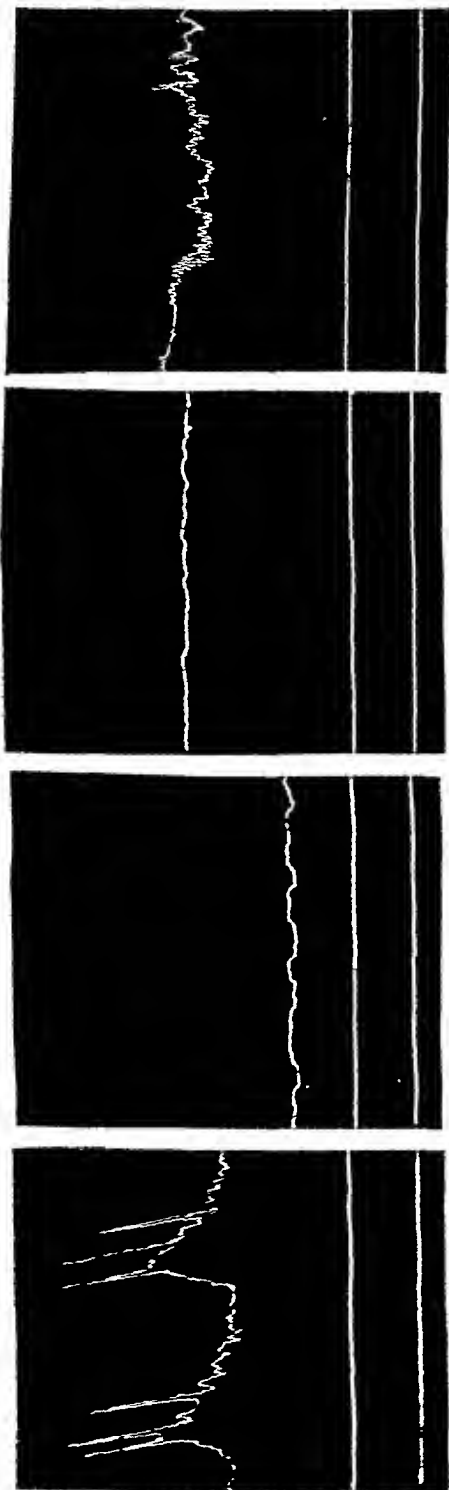


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an almost immediate cessation of rectal contractions. Figs. 10-20 show the results of these studies. It is to be noted that pentobarbital and  $MgSO_4$  have quite a prolonged action in inhibiting contractions; whereas, the action of atropine is over at the end of one hour. A relatively small dose of calcium gluconate given intravenously to one animal failed to inhibit contractions. In another animal it was shown to reverse the inhibiting action of  $MgSO_4$ .

#### DISCUSSION

The results obtained in these experiments confirm those of Popielski and others. They indicate that in the dog the celiac, superior and inferior mesenteric ganglia are an essential element in the normal functioning of the gastrointestinal canal and that they exercise a restraining influence on its activities. The watery diarrhea immediately after ganglionectomy when the animals were fasting points to a marked secretory activity of the intestine. This confirms previous observations on the cat by Wright and co-workers<sup>7</sup> where it was shown that the celiac ganglia constitute an important brake on the secretory function of the duodenum and small intestine. That mucus was passed in large amounts is explained by the work of Wright, Jennings, and Florey.<sup>8</sup> These authors demonstrated that the nervi erigens is a powerful secretory nerve; whereas, the postganglionic fibers from the inferior mesenteric ganglion inhibit the secretion of mucus by the colon.

Passage of blood during the days immediately following operation came at the end of defecation and was always associated with tenesmus and straining, which suggests that it was related to spasm of the lower colonic segment. The absence of ulcers and erosions in the colon of animals that passed blood just before death suggests that the blood had its origin in capillary hemorrhage and was related to the intramucosal hemorrhages found at autopsy. In previous communications<sup>9, 10</sup> it has been shown that hemorrhage can be produced from an explant of dog's colon by agents capable of initiating severe spasm. The mechanisms by which spasm produces hemorrhage from the mucosal surface is not clearly understood. Since the blood vessels to the mucosa must traverse the powerful circular and longitudinal muscles of the intestine before reaching their destination, they can be completely occluded when these muscles contract.

Spasm of the intestinal muscles at first may close the exit for the blood through the veins and then through the arteries, thus trapping a large reservoir of blood in the dilated capillary bed of the mucosa. Further spasm may exert such a powerful pressure on the vessels that they rupture, a possible explanation for the erosions and intramucosal hemorrhages seen after inducing spasm by a great number of agents (dysentery toxin,<sup>5</sup> pilocarpine,<sup>11</sup> physostigmine and acetyl choline,<sup>10</sup> and barium chloride<sup>12</sup>). Another possibility is the production of severe anemia by the muscle spasm and a resulting death of the mucosal cells

Studies with the balloon revealed a constant increase in rectal contractions after operation and indicate that the diarrhea was dependent on an increased irritability of the gastrointestinal tract to the normal stimulus of the feces. The absence of such increased contractions during the diarrhea due to horse meat suggests that there are two distinct mechanisms for diarrhea in the dog.

The importance of finding peptic ulcerations in these animals cannot be evaluated without further study. Similar results were noted by Popielski, Laignel-Lavastine, and Grundelfinger. The observations of the last author must be discounted, however, for he considered the normal mucosal depressions in the dog's duodenum as ulcerations. Volini and associates<sup>13</sup> have demonstrated that these apparent defects are actually covered by normal mucosa. Donati found little evidence of mucosal damage in his dogs, but he only resected the left celiac ganglion, a procedure which also yielded negative results in the hands of Grundelfinger. Ivy<sup>14</sup> reported no ulcers in dogs after dividing the splanchnics or removing the celiac plexus.

The effect of stimulating the vagi theoretically should give much the same result as removal of the celiac ganglia. Stahnke<sup>15</sup> observed defects in the mucous membrane over the lesser curvature in two of five dogs that had chronic stimulation of the vagi.

The experiments on rabbits have been contradictory, the same procedure giving quite different results in the hands of various investigators. Hemorrhagic erosions of the stomach have been described both after bilateral vagotomy and resection of the celiac plexus. Others obtained negative results with these procedures. The reader is referred to the work of Talma,<sup>16</sup> Donati,<sup>4</sup> Durante,<sup>17</sup> Van Yzeren,<sup>18</sup> and Alvarez.<sup>19</sup>

In dogs with severe diarrhea emaciation develops rapidly. Weech and Paige<sup>20</sup> have shown that protein deficiency in dogs is often associated with peptic ulcers. Keller<sup>21</sup> autopsied 150 undernourished dogs and found round, hemorrhagic craters in the stomach of ten animals. These considerations make it impossible to say definitely whether inanition or prevertebral ganglionectomy was responsible for the peptic ulcers in these experiments.

The antispasmodic action of pentobarbital as demonstrated in these experiments confirms the previous observations of others on members of the barbiturate group.<sup>22-25</sup> The similar effect of parenteral  $MgSO_4$  was first investigated by Meltzer and Auer<sup>26</sup> and more recently by Straub and Schild<sup>27</sup> and Kanda.<sup>28</sup> In our experiments these agents evidenced an antispasmodic action of at least two hours. The antispasmodic action of these two agents has been shown to be a peripheral one (26,  $Mg$ ; and 23, pentobarbital).

*Clinical Implications.*—The finding of diarrhea and mucus in the animals subjected to prevertebral ganglionectomy has a bearing on so-called mucus colitis. Jones and White<sup>29</sup> call attention to the neurogenic factors

in this disorder and to the fact that parasympathetic stimulation reproduces the essential elements of the disease. The experiments here reported suggest that underactivity or lack of sympathetic control to the colon may well lead to the same result as actual parasympathetic stimulation of that organ.

The association of tenesmus with rectal bleeding in these experiments has a bearing on one aspect of ulcerative colitis. On careful questioning one can invariably elicit the story that the patients know beforehand when blood will appear in the stools. Severe lower abdominal cramps, tenesmus, and a dull or sharp ache in the rectum preface the appearance of blood. These are all symptoms associated with severe muscle contraction.

The efficient antispasmodic action of pentobarbital and  $MgSO_4$  suggests their use in clinical conditions associated with severe muscle spasm such as acute ulcerative colitis.<sup>30</sup>

#### SUMMARY

1. When the celiac and superior and inferior mesenteric ganglia are removed in dogs there result a foul diarrhea, with mucus and blood in the stools and increased rectal activity as measured with a balloon.

2. At autopsy four of nine animals subjected to this operation showed peptic ulcers, one of which had perforated. These ulcers may be due to inanition rather than the ganglionectomy.

3. Other changes noted were intussusception, gastritis, duodenitis, enteritis, hyperemia, edema of the intestine, and intramucosal hemorrhages. A possible explanation for the appearance of these lesions has been offered.

4. It was shown that  $MgSO_4$ , pentobarbital, and atropine all relax the colon when given intravenously in large doses; calcium does not, but reverses the effect of magnesium.

5. The relationship of these findings to various clinical problems has been discussed.

The author appreciates the suggestions and help offered by Dr. Walter B. Cannon and Dr. Joseph C. Aub. Thomas Barnett gave valuable technical assistance.

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# LARGE ISLET-CELL TUMOR OF THE PANCREAS

ALEXANDER BRUNSCHWIG, M.D., CHICAGO, ILL.

*(From the Departments of Surgery and Medicine of the University of Chicago)*

THE successful excision of islet-cell tumors of the pancreas has now been accomplished with sufficient frequency to render perhaps unwarranted the report of a single rather typical case. Whipple and Frantz<sup>1</sup> have reviewed the literature up to 1935 and in a more recent summary Whipple<sup>2</sup> states that he has collected 110 cases (including 15 cases of his own) of hypoglycemia with pathologically proved islet-cell tumors. Eighty-two were removed by surgeons at operation, of which 69 survived; 3 died within six months of carcinoma of islet tissue with metastasis. The neoplasms were usually 1 or 2 cm. in diameter and not infrequently multiple. In one case reported by O'Leary and Womack<sup>3</sup> (Case III), the neoplasm was quite large, measuring 11 by 9 by 9 cm. and weighing 500 Gm.

The following case was thought worthy of recording because of the very large size of this type of tumor (largest yet reported) and because its successful resection again illustrates how radically one may operate upon the pancreas in man.

## CASE REPORT

G. P. L. (No. 233821), white, male, aged 32 years, traveling salesman, was admitted to the University of Chicago Clinics Jan. 1, 1940. The present complaints began in April, 1939, when he had a two-hour period of amnesia during which he performed actions automatically. Four days later he experienced an attack of syncope in the street and was revived in a hospital by injections of glucose. Subsequently there were many attacks, characterized by convulsive seizures and periods of stupor. Glucose relieved the attacks and increased food taking diminished their frequency and intensity. In September, 1939, he was hospitalized in another institution where as a result of study a diagnosis of islet-cell, insulin-producing tumor was made and laparotomy was performed. The pancreas was exposed and a tumor mass, measuring about 6 or 7 cm. in diameter, was found at the junction of the body and tail; adjacent to it was a second tumor measuring about 1.5 cm. in diameter. A specimen removed from each mass for frozen section was reported as "adenocarcinoma, Grade III." The abdomen was then closed.

Following operation the attacks continued but by frequent feedings were reduced in severity and frequency, there being a six-week period in which no attacks occurred. These increased feedings resulted in a gain of 25 pounds in weight. During the ten days prior to admission attacks would occur at about 11:00 A.M. but would be aborted by drinking orange juice.

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The history was otherwise irrelevant except for the fact that six aunts and uncles on the father's side, the mother and maternal grandmother, and one maternal uncle had died of malignant neoplastic disease.

Physical examination revealed a well-developed obese young adult male weighing 252 pounds, 6 feet in height, mentally alert, and apparently in no discomfort. There were no palpable masses through the thick abdominal wall and no superficial adenopathy. X-rays of the lungs revealed no metastases. An x-ray film of the abdomen showed a large rounded soft tissue mass in the left upper quadrant with small calcium shadows in it. Fasting blood sugar was 48 mg. per cent and following the standard dextrose tolerance test rose to 152 mg. per cent one-half hour after taking dextrose solution, 195 mg. per cent at one hour, 49 mg. per cent at two hours, and 36 mg. per cent at three hours.

I witnessed the onset of an attack at about 11:00 A.M. following breakfast at 8:00 A.M. the morning of admission. The eyes became "glassy," the face flushed, and the patient, with a peculiar staring expression, was unresponsive to questions. Drinking 200 c.c. of a concentrated dextrose solution resulted in a few moments in the return of normal expression and usual keen mental alertness.

It was felt that another laparotomy was indicated to remove the pancreatic tumor if possible, since the general well-being of the patient and the fact that the history of the attacks showed they were not increasing in severity suggested that the neoplasm might not have metastasized. This was performed on Jan. 4, 1940, under nupercaine spinal and ethylene-ether anesthesia. The upper abdomen was entered through an inverted T-incision (Fig. 1). A large mass surrounded by dense adhesions was encountered in the body of the pancreas. Palpation of the liver and exploration of the general peritoneal cavity revealed no gross evidence of metastases. Freeing of the tumor mass was begun by severance of adhesions from the gastrocolic omentum and transection of this. The upper aspect of the tumor mass was adherent to the posterior wall of the stomach. This was freed by cutting away the external muscular coat of the stomach wall over a surface of about 5 by 8 cm. Using the normal size spleen as a handle for the mass, the latter was then brought into the operative wound and finally freed of all adhering tissue except at two points; namely, its junction with the pancreas and over an area about 2 cm. in diameter with the first loop of jejunum. Fearing the latter was a point where tumor cells had infiltrated the wall, the adherent segment was resected. The tumor and spleen were then removed by cutting transversely through normal appearing pancreas (and splenic vessels) about 2 cm. away from the gross limits of the tumor. When the latter step was completed, it was observed that of the pancreas, the head and about 2 cm. of the neck remained. The cut surface of pancreas was sewed over with a continuous suture of fine silk. What was thought to be the main pancreatic duct was ligated separately. Just proximal to the running suture a silk ligature was passed completely around the pancreatic stump and tied snugly. The abdomen was closed in layers with interrupted silk and silver wire tension sutures. A small soft rubber drain was inserted to the large tumor bed.

Subjectively the patient felt quite well during all of the postoperative period. The drain was removed forty-eight hours after operation and in a few days the small amount of serous discharge from the drain tract ceased and the latter closed spontaneously. The night of the operation the temperature rose to 104° F. rectally. A moderate icterus developed on the sixth day but by the fifteenth day had disappeared.

Twenty-four hours after operation the blood sugar was 560 mg. per cent with no acetone or diacetic acid in the urine. One hundred units of insulin were given throughout the first day and the next morning the blood sugar was 299 mg. per

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### CASE REPORT

G. P. L. (No. 233821), white, male, aged 32 years, traveling salesman, was admitted to the University of Chicago Clinics Jan. 1, 1940. The present complaints began in April, 1939, when he had a two-hour period of amnesia during which he performed actions automatically. Four days later he experienced an attack of syncope in the street and was revived in a hospital by injections of glucose. Subsequently there were many attacks, characterized by convulsive seizures and periods of stupor. Glucose relieved the attacks and increased food taking diminished their frequency and intensity. In September, 1939, he was hospitalized in another institution where as a result of study a diagnosis of islet-cell, insulin-producing tumor was made and laparotomy was performed. The pancreas was exposed and a tumor mass, measuring about 6 or 7 cm. in diameter, was found at the junction of the body and tail; adjacent to it was a second tumor measuring about 1.5 cm. in diameter. A specimen removed from each mass for frozen section was reported as "adenocarcinoma, Grade III." The abdomen was then closed.

Following operation the attacks continued but by frequent feedings were reduced in severity and frequency, there being a six-week period in which no attacks occurred. These increased feedings resulted in a gain of 25 pounds in weight. During the ten days prior to admission attacks would occur at about 11:00 A.M. but would be aborted by drinking orange juice.

tologic structure. In the central portion of the mass (Fig. 3A) the tissue was very sclerotic, being composed of dense hyalinized anastomosing bands, the interstices of which contained small cords of epithelial cells. There were areas of calcification but no ossification of the hyalinized tissue. Sections taken from elsewhere especially from the more peripheral portions of the tumor (Fig. 3B), showed it to be composed of dense sheets of small epithelial cells with varying shape. The cytoplasm appeared for the most part finely granular and the nuclei moderate in size and fairly hyper-



FIG. 2.—Photograph of bisected formalin-fixed islet-cell tumor of the pancreas, showing solid structure throughout. Excised portion of normal pancreas is seen just below the point of the arrow; above this is the segment of outer muscular coat of the posterior wall of the stomach removed with the tumor because of the intimate adherence of the latter. C, Calcification in most fibrotic portion of the tumor.

cent. The daily dose of insulin varied from 55 to 70 units for the next eleven days on a 1,200 to 1,500 calorie diet; it was reduced to 20 units a day for the next eleven days, the fasting blood sugars being within normal limits. He was discharged from the hospital Feb. 1, 1940, the fasting blood sugar being 95 mg. per cent without insulin (1,500 calorie diet) the previous day and a normal dextrose tolerance test being obtained. There was no evidence of insufficiency of external pancreatic secretion, the stools being normal except on one occasion when there was a copious, very foul stool. By April 1, 1940, he had resumed his occupation and has remained free from attacks. He was last seen on Dec. 1, 1940, in apparent good health.

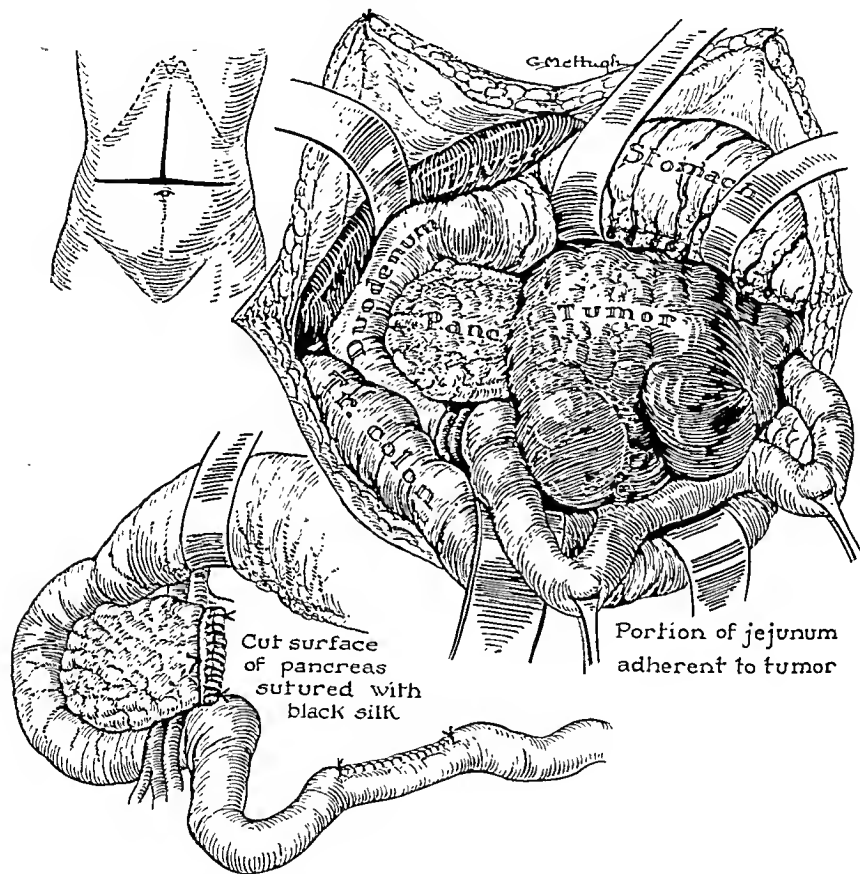


Fig. 1.—Semidiagrammatic representation of operative findings in case reported in the text showing site and relative size of islet-cell tumor, type of incision in the abdominal wall, and treatment of the pancreatic stump after excision of the neoplasm and adherent portion of jejunal wall.

*Pathologic Study.*—The gross specimen consisted of a spherical nodular tumor mass 15 cm. in greatest diameter by 13 by 10 cm. (Fig. 2). Its capsule appeared intact. Attached at one point was a tongue of normal appearing pancreas 2 by 1.5 by 1.5 cm. The cut surface of the tumor was fibrotic, yellow streaked, and dull granular in appearance with several enleareous deposits in the center of the mass. It weighed 673 Gm.

Microscopic examination of sections stained by hematoxylin and eosin taken from various portions of the tumor mass showed considerable variation in his-

chromatic. In many areas the cells had assumed a rather tall or low columnar appearance and were arranged about small lumina or tended to an acinar organization. Mitotic figures were infrequent. In cross sections of some of the larger veins, masses of tumor cells may be seen within the lumina.

Supravital stains with Janus green and with neutral red were made by Dr. Sylvia Bensley, of the Department of Anatomy. Such stains color selectively the granules of the beta cells. Most of the cells in the sections did not contain granules which stained with these vital dyes, although there were scattered cells which gave a typical beta cell picture. Since, however, the patient had exhibited the typical attacks of hyperinsulinism, it is a justifiable conclusion that in some portions of the tumor there were probably masses of functioning beta cells (neoplastic).

Sections through the segment of excised adherent jejunum showed the presence of typical normal pancreatic tissue, including islets in the jejunal wall extending through to the submucosa. There was a large duct leading from the intramural pancreas into the jejunal lumen. In my opinion this abnormal location of the pancreatic tissue may well represent a grafting of pancreatic tissue from the normal site onto the bowel wall that occurred inadvertently at the previous operation when packs had been placed at the sites of biopsy of the tumor and subsequently, of course, pulled out. The protocol of the first operation made no mention of jejunum being adherent to the tumor or pancreas.

*Pathologic Diagnosis:* Islet-cell tumor of the pancreas. Taking into consideration the history and gross findings at operation, it is impossible to state whether the neoplasm was benign or malignant.

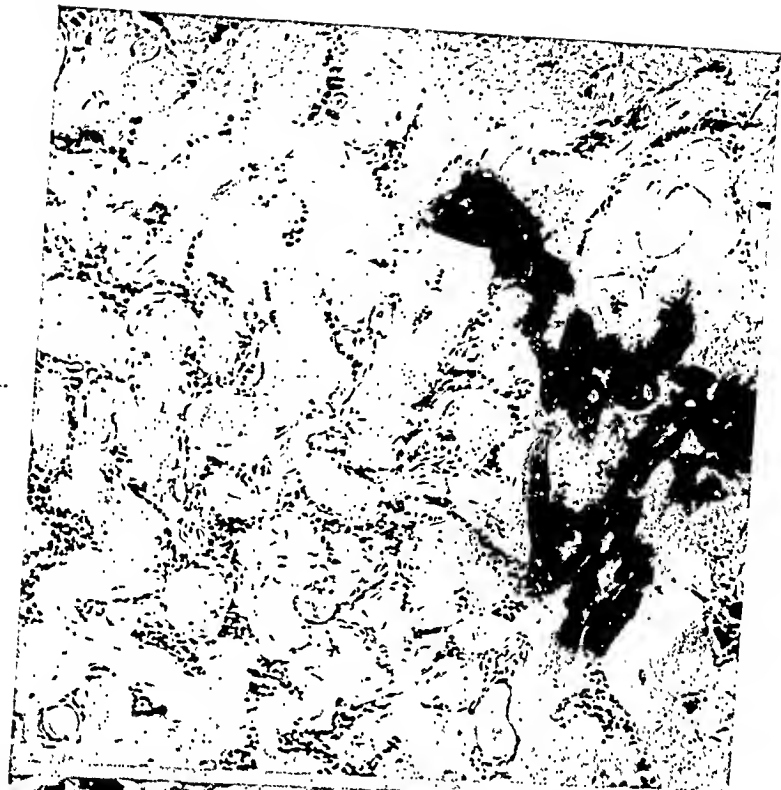
#### DISCUSSION

The above case would appear to be of interest because of the unusually large size of the tumor and its rapid growth from about 7 cm. in diameter to 15 cm. in diameter over a period of four months without gross evidence of metastases during this period. This increase in size was not accompanied by a parallel increase in number or severity of attacks as more judicious spacing in the food intake resulted in a fair degree of control of the attacks. This might also indicate a variation in the insulin output of the tumor as a whole due to varying functions in this respect on the part of the tumor cells. From the recorded experience with these tumors it would appear that much smaller neoplasms than the one reported above secreted as large or larger amounts of insulin.

The postoperative diabetes might be accounted for on the basis of relative inactivity of the islets remaining in the normal pancreas tissue due to the large output of insulin from the tumor and by the fact that, when the latter was suddenly withdrawn, the remaining normal pancreas was not prepared to cope with the sudden increased demands upon it. That recovery of adequate function in respect to insulin production did occur is attested to by the fact that after approximately three weeks injections of insulin were not necessary to maintain normal blood sugar levels.

A study of the sections would certainly warrant the diagnosis of malignant neoplasm on morphologic criteria alone. However, from

A.



B.

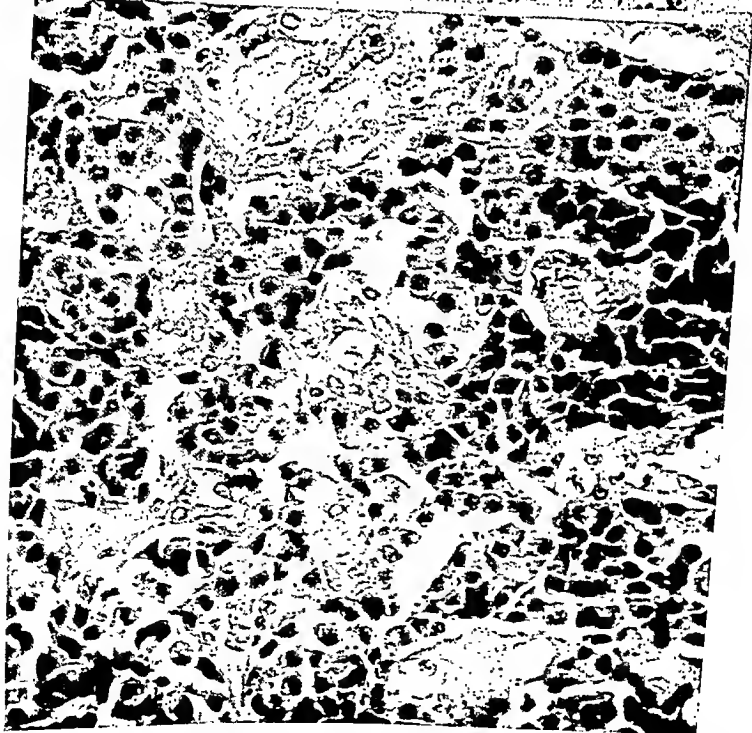


Fig. 3.—A. Photomicrograph (X110) of central portion of islet tumor of pancreas, showing dense sclerotic tissue throughout which are scattered irregular cords of tumor cells. A large calcareous deposit is also shown. B. Photomicrograph (X450) from area in periphery of tumor, showing dense cellular nature of the tumor in this region. The tumor cells vary in size and shape and suggest a rapidly growing process.

## STRANGULATED HERNIA REDUCED EN MASSE

DANIEL CASTEN, M.D., AND MILTON BODENHEIMER, M.D.  
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*(From the Surgical Service of the Hospital for Joint Diseases)*

THE reduction en masse of a strangulated inguinal or femoral hernia is an extremely rare occurrence. From 1702, when this entity was first described by Saviard, until 1931 Pearse,<sup>1</sup> was able to collect only 190 cases, including 1 of his own. Conner and Hewitt<sup>2</sup> reported 5 cases of reduction en masse occurring in a series of 1,618 cases of strangulated hernia, an incidence of 0.3 per cent. Pearse states that the incidence is approximately 1 in 13,000 cases of inguinal hernia. Since this exhaustive report by Pearse, a total of 15 cases has been added to the literature, as follows: Nason and Mixter, 5 cases;<sup>3</sup> Dunn, 1 case;<sup>4</sup> St. John, 3 cases;<sup>5</sup> White, 1 case;<sup>6</sup> Vail, 1 case;<sup>7</sup> Del Toro, 1 case;<sup>8</sup> Druckerman, 1 case;<sup>9</sup> Abell, 2 cases.<sup>10</sup> The reduction en masse of a femoral hernia is much more unusual than the inguinal type, a total of only 25 cases having been reported to date. We are presenting 2 cases (1 inguinal and 1 femoral) which demonstrate several points of interest.

### CASE REPORTS

CASE 1.—W. C. (No. 75032), was admitted to the surgical service of the senior author (M. B.) on Feb. 12, 1939. He gave a history of intermittent, colicky abdominal pain for one hour. About six hours before admission the patient noted a large swelling in the right scrotum which he forcibly reduced. He had noted a mass in this area for the past five years, but it had never been as large as on this occasion. Eighteen years previously the patient had had a right femoral hernioplasty.

On admission the temperature was 98.4° F.; the pulse rate was 60 per minute; and the respirations were 20 per minute. There was moderate lower abdominal tenderness present but no distention. There were no masses palpable, either abdominally or rectally. The right external abdominal ring was enlarged, and a slight impulse was transmitted through the inguinal canal to the examining finger on coughing. The patient developed further signs of intestinal obstruction while under observation, and a scout film of the abdomen revealed fluid levels, indicating intestinal obstruction.

A preoperative diagnosis of intestinal obstruction due to reduction en masse of a strangulated hernia or to a strangulated internal hernia was made, and an operation was performed by Dr. B. N. Berg twelve hours after admission. A right rectus muscle-splitting incision was made. The small intestines were found to be greatly dilated. In the right lower quadrant of the abdominal cavity a mass about 4 inches in diameter was observed. This was extraperitoneal and bulged into the peritoneal cavity. Two limbs of small intestine emerged from this mass, and a constriction was found which had strangulated the bowel. Further exploration determined that the constriction was at the internal abdominal ring. The ring

the biologic standpoint the absence of metastases while the primary tumor grew so rapidly in a relatively young adult would favor the view that the process was, up to operation at least, actually benign, or at least still localized. Previous experience with these tumors has shown that, while they might appear malignant histologically, removal of such growths has resulted in prolonged survival without recurrence of attacks of hyperinsulinism.<sup>4</sup> At the first exploration, two tumor masses were observed. These apparently had fused to form the large tumor found at the second operation. While the smaller tumor might have been a local metastasis, it is equally probable that at the onset there were two distinct neoplasms arising from different islets.

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was divided, and about 6 inches of bowel were withdrawn into the peritoneal cavity. The bowel was viable. A simple purse-string closure of the neck of the sac was performed, and no further attempt was made to repair the hernia. The abdomen was closed in layers. During the closure of the peritoneum it was noted that this structure was extremely relaxed in the right inguinal region. Convalescence was uneventful, and the patient was discharged on the sixteenth postoperative day.

CASE 2.—A. V. (No. 75506), was admitted to the private service of one of us (D. C.) on March 11, 1939. On admission the patient gave a history of severe, colicky abdominal pain associated with vomiting and obstipation for three days. At the onset the vomitus contained old food particles, but it had become fecal in character prior to admission to the hospital. The patient had had a right inguinal hernia repaired fifteen years previously and this had not recurred, but a mass had been noted in the right groin below the old scar on several occasions since the operation. The mass, however, had not been noted for several days preceding the onset of the present illness.

Examination revealed an acutely ill patient evidently in severe distress. The temperature was 98.6° F.; the pulse rate was 86 per minute; and the respirations were 20 per minute. The blood pressure was 128 mm. systolic and 78 mm. diastolic. The abdomen was moderately distended, and tenderness was elicited in both lower quadrants. No rebound tenderness or abdominal rigidity was noted. No masses were palpable either by abdominal or rectal examination. There was a well-healed right inguinal hernia scar with no evidence of recurrence of the hernia. No femoral hernias were noted. The blood examination revealed the following: red blood cells, 6,016,000 per cubic millimeter; hemoglobin, 19 Gm.; white blood cells, 12,900 per cubic millimeter. The differential count showed 71 per cent neutrophils and 29 per cent lymphocytes. The blood findings indicated a marked hemoconcentration. The urine was normal.

A preoperative diagnosis of acute intestinal obstruction was made, with etiology unknown. Laparotomy was performed three hours after admission through a right rectus muscle-splitting incision. A small amount of serosanguineous fluid was found in the peritoneal cavity. The entire jejunum and upper ileum were markedly dilated, and the bowel wall was thick, edematous, and dark reddish to purple in color. There was a mass about 6 cm. in diameter in the right lower quadrant of the abdominal cavity; it was properitoneal in position and produced a definite bulge into the peritoneal cavity. Two loops of small intestine emerged from an opening in this mass, and a marked constriction of the bowel had occurred at this point. The constricting ring was divided, and about 8 inches of bowel were withdrawn and replaced in the abdominal cavity. Further exploration revealed the sac to be a femoral hernial sac which had been reduced en bloc. The femoral opening appeared to be enlarged while the internal abdominal ring was found to be quite small. The bowel was viable. Because the condition of the patient was very precarious, a simple purse-string suture closure of the neck of the sac was performed without excision and the abdomen was closed in layers. A transfusion of 500 c.c. of citrated blood was given on the operating table. Thirty-six hours postoperatively the patient developed a temperature of 108° F. which persisted for three hours, but this returned to normal in the ensuing twenty-four hours. Otherwise the convalescence was uneventful, and the patient was discharged on the fifteenth postoperative day. Examination three months after the operation revealed the presence of a right femoral hernia.

#### DISCUSSION

The reduction of a strangulated hernia en masse is, in fact, an apparent reduction whereby the sac or a rim of the sac and the incarcerated

contents are displaced from their accustomed position in the inguinal or femoral canals to an anomalous position which is usually properitoneal. During this reduction the relation of the constricting neck of the sac to the contents is undisturbed, even in those cases in which partial rupture of the sac occurs. An attempt at forceful reduction of a strangulated hernia is the usual cause of this apparent reduction, but frequently it may occur spontaneously and even without the knowledge of the patient (our Case 2; Nason and Mixer, Case 1). In many cases a history of repeated reductions of the hernia by taxis may be elicited, with the last reduction being the most difficult of accomplishment. A considerable proportion of these cases occur in recurrent hernias or in patients who have had a previous operation for an inguinal or femoral hernia.

The exact mechanism of reduction en masse is not thoroughly understood, and several theories have been offered to explain this occurrence. It is generally accepted, as pointed out by Nason and Mixer, that certain conditions must obtain before reduction en masse can occur: (1) the neck of the sac must be sufficiently small to retain and incarcerate the contents, (2) the sac must be freely movable in the inguinal or femoral canals and not attached firmly to any of the structures in these canals, and (3) the neck of the sac must be sufficiently mobile and detached from the internal ring (in inguinal hernias). Unless these conditions are present, a reduction en masse cannot take place and the strangulated hernia either will be reduced completely and satisfactorily or will remain as an irreducible strangulation.

One theory advanced to explain the mechanism of false reduction is that the presence of a large preformed properitoneal space, such as might be due to excessive properitoneal fat, is a predisposing cause. In Case 1 of our series the surgeon noticed an extremely lax peritoneum which would account for the presence of a large properitoneal space. Pearse<sup>1</sup> suggests that in many cases a combined or bilocular sac is present, consisting of an inguinal pouch and a properitoneal pouch. In these cases the strangulated bowel can be displaced from the inguinal to the properitoneal pouch. He states that in 15.5 per cent of the recorded cases such an inguinal properitoneal sac was present with the strangulated intestine in the properitoneal portion. He also states that in 77.3 per cent of the cases the entire sac and contents were displaced to a properitoneal position.

It is our belief that the reduction of a strangulated inguinal hernia en masse depends on the relationship between the internal abdominal ring and the neck of the sac. Ordinarily, attempts at reduction of a strangulated inguinal hernia will result in (1) complete and satisfactory reduction, (2) no reduction and persistence of the external position of the strangulated hernia, or (3) reduction en masse. The result will

depend in large measure on the resistance offered to reduction by the transversalis fascia at the internal ring and the constricting neck of the sac. If neither of these constrictions is exceptionally tight, a complete and satisfactory reduction will occur. If both remain firm, attempts at reduction will fail and the strangulation will persist. If, however, the constriction of the neck of the sac is unyielding, while the internal ring is lax, a reduction en masse will occur, providing, of course, that the three conditions enumerated above as prerequisite for this occurrence are present. When a hernia has been present for some time and has been reduced frequently, it is not unusual to find a relaxed internal ring with separation of the transversalis fascia from the layers of the sac. In fact, the transversalis fascia may be extremely attenuated at this point. When strangulation supervenes in a case of this kind, it is probably caused by fibrosis and stricture of the neck of the sac alone and bears no relation to the relaxed internal ring; a situation is set up wherein reduction en masse can occur. When the strangulation occurs at the external abdominal ring, the above circumstances undoubtedly do not prevail because of the firmness of the arched fibers of the external oblique aponeurosis forming this ring. It is probable that with this type of strangulation reduction en masse rarely occurs because the primary constricting factor is the aponeurotic structure and not the neck of the sac. Inasmuch as a great percentage of strangulations occur at the external ring, this may explain the rare occurrence of reduction of a strangulated hernia en masse.

#### DIAGNOSIS

The history and symptomatology in a typical case afford the surest means of establishing a correct diagnosis. Usually the hernia has been present for many years and has been successfully reduced many times during this period. Frequently a history of an operation for an inguinal or femoral hernia may be obtained. As a rule, the last reduction was accomplished only after excessive manipulation and probably was accompanied by pain; finally, the expected relief of the symptoms of strangulation did not occur. This is the usual story and, when obtained in conjunction with symptoms of vomiting, colicky abdominal pain, and obstipation, the diagnosis readily follows. In many cases, however, the typical sequence of events does not occur. The patient may have been completely unaware of the presence of a hernia, and consequently no history of taxis is obtained. In other cases the hernia is reduced with great ease or reduces itself spontaneously. In cases of this type the inguinal or femoral rings are undoubtedly relaxed, and the strangulation is due to fibrosis and stenosis of the neck of the sac. Another finding which occasionally obscures the diagnosis is the period of temporary respite from symptoms immediately following the reduction en masse. This period may last from a few hours to several weeks and is sufficient

in many instances to obliterate from the patient's mind the memory of the reduction of the hernia. As a result the symptoms of intestinal obstruction, when they do occur, are not associated with a strangulated inguinal or femoral hernia, and the correct diagnosis is not made.

The common sequence of events may then be briefly summarized as follows:

1. An inguinal or femoral hernia has been present for several years and may have been operated upon previously.
2. This hernia has become incarcerated several times but has always been reduced by manipulation.
3. The last reduction was accomplished with more difficulty and was accompanied by pain.
4. The symptoms of intestinal obstruction do not subside as expected or subside for only a brief interval.

Physical examination, except for establishing the fact that intestinal obstruction is present, rarely aids in establishing the etiological factor in cases of reduction en masse. Moderate abdominal distention is usually present, and tenderness over the lower quadrants of the abdomen may be elicited. A mass may be palpated occasionally by abdominal or rectal examination, but this is a relatively uncommon finding. The palpation of an abdominal mass with the examining finger in the inguinal canal is very significant, especially when a pertinent history has been obtained. Very frequently the external abdominal ring is enlarged. Nason and Mixer point out that a definite defect is commonly noted in the inguinal canal with only a very feeble impulse transmitted to the examining finger on coughing.

#### TREATMENT

The treatment of reduction en masse of a strangulated hernia is surgical. With intestinal obstruction of the strangulating type, treatment by suction with either the Wangenstein or the Miller-Abbott tube is definitely contraindicated. After preliminary treatment to restore the fluid and electrolyte balance, immediate laparotomy should be undertaken. We feel that in all cases the incision of choice is a muscle-splitting rectus incision. When doubt as to the diagnosis is present, this incision will probably be employed, but it is indicated likewise in those cases in which the diagnosis has been definitely established. Proper exploration and resection of the bowel, if necessary, are much more easily accomplished through this incision than through an oblique inguinal incision, and, if it is deemed advisable, a repair of the hernia may be carried out from within the abdomen. We believe that relief of the strangulating obstruction is the primary aim of therapy and that little time should be spent on repair of the hernia, particularly since many of these patients are in poor condition from an obstruction of several

days' duration. The strangulated bowel should be carefully examined because of the possibility of minute rupture of the bowel wall having occurred as a result of overenthusiastic attempts at reduction.

The postoperative treatment is that of any strangulated hernia. In this period Wangenstein suction may be employed to great advantage to prevent distention of a possibly damaged bowel. Parenteral fluids and transfusions are employed when indicated.

The mortality rate depends almost entirely on the length of time elapsing between the onset of obstruction and the operative relief of the obstructing mechanism. Pearse states that in a collected series of 164 cases of the inguinal type the mortality was 40 per cent, while in twenty-four cases of femoral hernia the mortality was 70 per cent. With early diagnosis and operation through a rectus or midline incision the mortality rate should be no higher than for strangulated hernias not complicated by reduction en masse.

#### SUMMARY AND CONCLUSIONS

1. Two cases of reduction en masse of a strangulated hernia are reported, making a total of 207 cases in the literature.

2. The mechanism of reduction en masse is discussed. A theory is presented which explains this occurrence on the basis of changing relationships between the internal abdominal ring and the neck of the sac.

3. The diagnosis is usually made on the basis of a history of reduction of an incarcerated hernia without subsidence of the symptoms of obstruction.

4. Treatment is always surgical. It is important that the abdomen be opened through a muscle-splitting rectus incision.

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# ACUTE COMPLETE OBSTRUCTION OF THE HEPATIC VEINS

## REPORT OF CASE SIMULATING AN ACUTE ABDOMEN

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OBSTRUCTION to the hepatic veins is a relatively uncommon condition, but perhaps it is not as unusual as we have been inclined to believe. In 1845 George Budd, Professor of Medicine at King's College, reported a case of a man who died in the King's College Hospital from idiopathic thrombosis of the hepatic veins. In 1899 Chiari, of Prague, described three similar cases of his own and reviewed the literature. Accordingly, on the Continent the condition is known as Budd's or Chiari's disease. In 1920 Hoover<sup>1</sup> reported some thirty cases from the literature since which time there have been quite a number of isolated cases reported.

A variety of causes may operate to result in obstruction to the hepatic veins. Pressure from without by tumors, gummas, enlarged glands, etc., may be found. Congenital malformations, particularly of the vascular bed, may be factors. Actual disease of the veins themselves, either inflammatory or neoplastic or cicatricial, may exist. A primary endophlebitis has been reported occasionally. Most frequently, however, the process is part of a more general one, involving the inferior vena cava and/or the portal vein with its tributaries. The condition also may be due to a septic embolus which has lodged somewhere in the vessel and resulted in thrombus formation.

Various chemical poisons may cause the condition. It is also seen with polycythemia vera, although cerebral or peripheral vessels are more commonly involved than intra-abdominal ones.

In discussing hepatic complications of polycythemia vera, Sohval<sup>2</sup> says: "Patients with polycythemia vera commonly consult a physician because of vascular thrombosis." He remarks upon the rarity of thrombosis of the hepatic veins in polycythemia vera but reports such a case with dyspnea, weakness, ascites, enlarged liver, jaundice, and fever. Occasionally, this condition is seen following splenectomy during the critical postoperative phase in which the thrombocytes arise to a very high level.

Apparently obstruction to the hepatic veins occurs more commonly in young people. Savin<sup>3</sup> gives the average age as 28.5 years. Sex seems to have no influence, for males and females show about the same incidence. The large majority of patients give no history of any definite symptoms previous to the onset of the obstruction.

Obviously a complete obstruction of the hepatic veins results fatally in a short time, and during this period there is marked passive congestion of the liver and spleen; in addition there are the findings associated with portal obstruction, such as edema of the wall of the intestine drained by the portal vein, ascites, etc. An incomplete or partial obstruction may cause complete fibrosis of the lobe or lobule of the liver involved, with symptoms similar to those found in complete obstruction but less severe.

Symptoms of this condition will depend upon the extent of the process. A mild degree of obstruction may cause no symptoms at all. A gradual or chronic type of obstruction will give rise to symptoms very similar to those occurring with portal cirrhosis. There will be epigastric distress, some enlargement of the liver and spleen, ascites, dilatation of collateral veins, etc.

The acute type, which seems to be the more frequent type encountered, comes on suddenly and may simulate closely some acute surgical lesion of the abdomen. The onset is usually abrupt with severe abdominal pain located in the upper abdomen; often there is persistent nausea and vomiting; there may be a slight icterus; elevation of the temperature may occur, but more frequently the temperature is subnormal; the pulse becomes rapid and the patient appears to have suffered a major abdominal catastrophe. Examination discloses an enlarged liver, the margin of which is tender but smooth; splenic enlargement may be made out if spasticity of the abdominal muscles permits; the abdomen is distended and hard; free fluid is usually present within the peritoneal cavity in varying amounts. The patient is bathed in perspiration and has a marked pallor. Occasionally, there may be a cyanosis of a lilac shade. The white blood count is usually markedly elevated with a preponderance of neutrophils. The urine may show evidence of renal irritation and perhaps a trace of bile. Commonly these patients with an acute obstruction become rapidly worse and die within thirty-six to forty-eight hours after the onset. It is easy to understand how a case presenting such symptoms may be considered a surgical problem and may be subjected to exploration. The literature does not record many such errors, but I believe this is due either to failure of recognition or to lack of interest. In discussing portal thrombosis, a closely associated condition, Pallette<sup>3</sup> describes a case in which the diagnosis of ruptured ectopic pregnancy led to exploration of the abdomen.

The diagnosis of obstruction of the hepatic veins is usually made post mortem, although there are a few confirmed reports of ante-mortem clinical diagnoses.

CASE REPORT.—D. M., a male, aged 26 years, entered the hospital on April 23, 1940, with the complaint of severe upper abdominal pain of forty-eight hours' duration and vomiting for twenty-four hours. The pain was described as cramplike and was located just below the xiphoid.

The patient's past history was essentially negative, although he had been "slowing up" for several months and had had a little indigestion. There had been no recent colds or dyspnea nor other possible exciting factors.

The present illness had commenced forty-eight hours previously with a crampy pain in the upper abdomen; later it became steady and generalized. Vomiting began twenty-four hours before admission and had been continuous. There had been some diarrhea for forty-eight hours, frequent watery stools without tenesmus.

The patient looked sick upon admission. His face was flushed, but he had a pinched expression. He was clear mentally and responded promptly to questions. The tongue was dry and coated. The sclera had an icteroid tinge. The heart and lungs appeared negative. The temperature was 103.6°; pulse, 140; respirations, 28; blood pressure, 118/76. The abdomen was distended throughout. There was marked tenderness in the upper half and rigidity of the entire abdomen. There was tympany in the midabdomen with dullness in both flanks. The liver dullness was noted not to be diminished and in fact was thought to be increased. Free fluid was detected in the flanks. Rectal examination was negative. The white blood count was 16,160. The urine showed a trace of albumin and a few red blood cells. No x-rays were made. Blood chemistry studies reported later showed a blood sugar of 33 mg.; N.P.N., 98 mg.; urea N, 41 mg. per 100 c.c. of blood. The blood Wassermann was reported negative. The clinical impression was that we were dealing with an acute abdomen, probably a perforated peptic ulcer.

The patient was prepared for operation and given 1,000 c.c. of 10 per cent dextrose intravenously.

An upper right rectus incision was made and enlarged later for exploration. As soon as the peritoneum was opened, there was a leakage of clear, bile-tinged fluid of which some 50 ounces were removed by suction. No perforation was found and no evidence of acute exudate noted. The liver and spleen were markedly enlarged, blue-black in color, smooth, and very hard. The mesentery and intestinal wall were edematous throughout; there were very many petechial hemorrhages in the serosa of both; the mesenteric glands were enlarged and the portal vein distended. Convinced that the condition was one of portal thrombosis, a biopsy of the liver was made and then the incision was closed.

Following operation, the patient became weaker, continued to vomit, and expired about twelve hours later.

A post-mortem examination showed the following interesting findings: There was about 2,500 c.c. of clear, straw-colored exudate in the peritoneal cavity. The diaphragm was pushed up to the level of the third interspace on the right and the fourth rib on the left. The mesenteric nodes were generally enlarged. The mesentery was edematous and its vessels congested. The pleural cavities contained about 300 c.c. of a fluid similar to that in the peritoneal cavity. The pericardial fluid was increased in amount and bile tinged. The right heart was dilated. The endocardium of the left ventricle showed petechial hemorrhages. The lungs were not remarkable. The spleen was greatly enlarged and mushroomed up against the diaphragm. The stomach and intestine showed some congestion but otherwise were negative. The liver was enlarged and weighed 2,300 Gm. Its surface was dark red and firm. Sections showed the liver markings to be obliterated and numerous pale areas were noted which had a yellow-green color. The large vessels throughout the liver were dilated. Their walls were thin and they contained blood clots within the lumina. The portal vein and its tributaries, the splenic and mesenteric veins, were dilated and filled with coagulated blood which was loosely attached.

Microscopic examination of the removed organs revealed interesting changes. The heart showed marked fragmentation of the muscle fibers; the fibers were swollen and edematous. Scattered throughout were numerous leucocytes, of which many were polymorphonuclears. Numerous sections of the liver were studied and these

Obviously a complete obstruction of the hepatic veins results fatally in a short time, and during this period there is marked passive congestion of the liver and spleen; in addition there are the findings associated with portal obstruction, such as edema of the wall of the intestine drained by the portal vein, ascites, etc. An incomplete or partial obstruction may cause complete fibrosis of the lobe or lobule of the liver involved, with symptoms similar to those found in complete obstruction but less severe.

Symptoms of this condition will depend upon the extent of the process. A mild degree of obstruction may cause no symptoms at all. A gradual or chronic type of obstruction will give rise to symptoms very similar to those occurring with portal cirrhosis. There will be epigastric distress, some enlargement of the liver and spleen, ascites, dilatation of collateral veins, etc.

The acute type, which seems to be the more frequent type encountered, comes on suddenly and may simulate closely some acute surgical lesion of the abdomen. The onset is usually abrupt with severe abdominal pain located in the upper abdomen; often there is persistent nausea and vomiting; there may be a slight icterus; elevation of the temperature may occur, but more frequently the temperature is subnormal; the pulse becomes rapid and the patient appears to have suffered a major abdominal catastrophe. Examination discloses an enlarged liver, the margin of which is tender but smooth; splenic enlargement may be made out if spasticity of the abdominal muscles permits; the abdomen is distended and hard; free fluid is usually present within the peritoneal cavity in varying amounts. The patient is bathed in perspiration and has a marked pallor. Occasionally, there may be a cyanosis of a lilac shade. The white blood count is usually markedly elevated with a preponderance of neutrophils. The urine may show evidence of renal irritation and perhaps a trace of bile. Commonly these patients with an acute obstruction become rapidly worse and die within thirty-six to forty-eight hours after the onset. It is easy to understand how a case presenting such symptoms may be considered a surgical problem and may be subjected to exploration. The literature does not record many such errors, but I believe this is due either to failure of recognition or to lack of interest. In discussing portal thrombosis, a closely associated condition, Pallette<sup>3</sup> describes a case in which the diagnosis of ruptured ectopic pregnancy led to exploration of the abdomen.

The diagnosis of obstruction of the hepatic veins is usually made post mortem, although there are a few confirmed reports of ante-mortem clinical diagnoses.

CASE REPORT.—D. M., a male, aged 26 years, entered the hospital on April 23, 1940, with the complaint of severe upper abdominal pain of forty-eight hours' duration and vomiting for twenty-four hours. The pain was described as cramplike and was located just below the xiphoid.

## SYPHILIS OF THE STOMACH NECESSITATING TOTAL GASTRECTOMY\*

C. HAROLD AVENT, M.D., MEMPHIS, TENN.

(From the Department of Surgery, the College of Medicine, University of Tennessee)

**S**YPHILIS of the stomach necessitating total gastrectomy is rare. Poole and Foster<sup>1</sup> reported the first case in 1931, and a thorough search of the literature fails to reveal any other similar case. It is interesting to note that total gastrectomy, an uncommon procedure and associated with a mortality rate of 40 to 50 per cent,<sup>2</sup> was successful in the case of Poole and Foster and in the one reported here.

### CASE REPORT

*History.*—R. S., a negro man, aged 31 years, was admitted to the medical service of the John Gaston Hospital on July 21, 1939, complaining of inability to "keep food down" of four months' duration. Vomiting at the onset of his present illness occurred at infrequent intervals, and the vomitus contained undigested food particles. The intervals between vomiting gradually shortened until the time of admission to the hospital, when all solid food was vomited soon after its ingestion. At no time in the course of his illness had the patient had pain. The most discomfort that he had ever felt was a sense of "fullness" which occurred just before, and was relieved by, vomiting. The patient stated that he had never vomited any blood nor had his stools been black.

Prior to the onset of the present illness he had never had any digestive disturbances of any description.

In 1933 the patient received "ten shots" for his blood, but the history of primary or secondary syphilitic lesions could not be obtained.

There was no evidence of syphilis obtained from the family history.

*Examination.*—Physical examination revealed a young negro adult showing a marked degree of malnutrition and dehydration. No further facts could be elicited by physical examination. The abdomen presented no palpable masses and no areas of tenderness.

The red blood cell count was 4,130,000 per cubic millimeter. The value for hemoglobin was 12 Gm. The white cell count was 7,950 per cubic millimeter, with lymphocytes, 25 per cent; neutrophils, 73 per cent; and eosinophils, 2 per cent. The Wassermann and Kahn reactions were positive.

Gastric analysis showed a complete absence of free hydrochloric acid and a total acid of three degrees.

*Roentgen Examination* (Dr. W. E. D. Anderson).—After the oral administration of barium sulfate roentgen examination showed a moderately dilated esophagus. The barium mixture entered the stomach readily, but, except for a faint trace, did not pass beyond the cardia. There was a funnel-shaped projection of barium,

\*The illustrations for this paper were prepared by Dr. J. L. Scianni, medical illustrator for the Department of Pathology, the College of Medicine, University of Tennessee.

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all showed widespread hemorrhage and necrosis. Small islets of relatively normal appearing liver parenchyma appeared about the portal triads. The central veins and the adjacent sinusoids were markedly engorged. The liver cells of the central part of the lobules were indistinct and leucocytic infiltration was evident. The portal veins were greatly distended with blood, but definite thrombosis of the smaller radicles was not observed. Some of the sections included large veins located near the periphery of the liver or outside of it. These veins all exhibited varying degrees of thrombophlebitis. One vein showed an organizing thrombus invaded by fibroblasts and attempts at canalization. Other large veins showed a fibrinous exudate adherent to the endothelium. In another section a large vein was seen partly filled by a thrombus showing fibroplastic organization.

#### DISCUSSION

The predominating pathology in this particular case would seem to be in the liver and takes the form of acute passive congestion of extreme degree with widespread hemorrhage and necrosis of the liver parenchyma. Such findings strongly suggest a sudden and complete blocking of the portal circulation proximal to the central veins of the liver. Sections show thrombophlebitis and complete thrombosis with beginning organization of the large veins of the liver. Grossly, the primary thrombosis was thought to be in the portal veins, but the existing changes in the liver can be more readily explained on a basis of obstruction of the hepatic veins.

The etiology of the thrombosis cannot be definitely determined. The acute onset in a person thought to have been previously well would seem to eliminate many of the possible etiological factors which are mentioned above. The post-mortem material fails to reveal any noteworthy evidence of such factors. The findings of acute myocarditis, cloudy swelling of the kidneys, and mesenteric lymphadenitis certainly suggest that infection did play an important role. Finally, we know that in certain instances no definite factor can be made out and such cases are described as idiopathic progressive thrombosis, of which this case may be an example.

#### CONCLUSIONS

A case of acute, complete thrombosis of the hepatic veins due to infection or idiopathic in origin is recorded with the principal post-mortem findings.

The patient had been subjected to exploratory laparotomy under the impression that the condition was an acute surgical emergency.

The literature of this condition is briefly reviewed.

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two-thirds normal size, its surface wrinkled. The curvatures of the stomach were almost obliterated by an infiltrating process which left the stomach a straight, thick, and leathery tube. The infiltration began about 2.5 cm. proximal to the pylorus and extended upward to the esophagus. The walls of the stomach were thick, and at the juncture of the body and cardia a complete stricture could be palpated. The esophagus was elongated and extended about 5 cm. below the diaphragm. Its transverse diameter was approximately twice normal (Fig. 2).

The adhesions between the left lobe of the liver and diaphragm were severed, and the left lobe was retracted; this allowed adequate exposure without severing the coronary ligament. The two curvatures were next freed, after dissecting the spleen from its attachment to the stomach, and the duodenum was cut across just distal to the pylorus (Fig. 3*A*). The distal end of the duodenum was closed, and the suture line buried in the peritoneum over the pancreas. The jejunum was then brought anterior to the transverse colon, and a point about 18 inches below the ligament of Treitz was selected for anastomosis to the esophagus. The stomach was used for traction while two posterior rows of sutures were taken between the esophagus and jejunum (Fig. 3 *B* and *C*). After the esophagus and jejunum were thus securely attached, the stomach was removed with about 5 mm. of esophagus and the end-to-side anastomosis completed. Enterointerostomy was not done (Fig. 3*D*). The abdominal wall was closed with through-and-through sutures of silk. The patient was given a 500 c.c. blood transfusion and returned to the ward in fair condition.

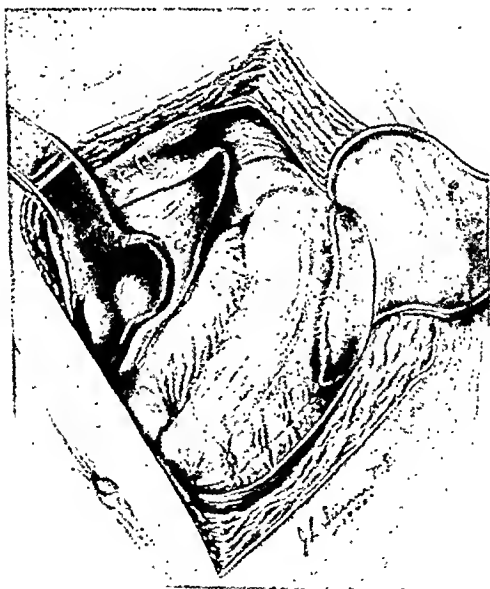


Fig. 2.—Drawing of the pathology in situ. The liver is smaller than normal; its surface is scarred; and adhesions fix its superior surface to the diaphragm. The adhesions to the left lobe have been severed, and the upper end of the stomach exposed. Note the thick, wrinkled, and straightened stomach with the enlarged spleen adherent to it.

*Pathologic Report* (Dr. W. A. D. Anderson) *Macroscopic*.—The specimen was a thick-walled tubular stomach measuring 14 cm. in length and 6 cm. in circumference (Fig. 4). At its thickest part the wall measured 8 mm. At the upper end of the specimen esophageal mucosa was evident and was white in color and relatively smooth. The esophageal mucosa merged, in an indefinite line, into the mucosa of the stomach. The gastric mucosa at this point was of a dark gray

smooth in outline, which extended into the body of the stomach for about 2.5 cm. The main portion of the body was markedly constricted. The funnel-shaped outline of barium was remarkably smooth. After further ingestion of barium sulfate it was noted that the cardiac orifice remained open and a considerable amount of the mixture was regurgitated into the widened esophagus (Fig. 1). Only a very small amount of barium trickled through the strictured area of the stomach. After six hours there was about 90 per cent retention of barium above the stricture.

Dr. Anderson concluded from his roentgen examination that the gastric lesion was benign.

In consultation with the Medical Service I advised surgical relief of the obstruction, but the patient declined the operation and signed his release from the hospital on July 27, 1939.

On Aug. 30, 1939, the patient returned to the hospital and was admitted to the Surgical Service. The amount of food tolerated was considerably less than it had been one month previously. Only fluid in small quantities was retained. His weight was 116 pounds, which was 70 pounds below normal. Dehydration was marked.

The patient was prepared for surgery by the parenteral administration of dextrose, physiologic saline solution, and vitamin concentrates.



Fig. 1.—Roentgenogram shows almost complete obstruction at the juncture of the fundus and body of the stomach. The arrows mark the esophagogastric union. Note the lengthening and dilatation of the abdominal esophagus which was interpreted as gastric fundus before operation.

*Operation.*—On Sept. 6, 1939, under intratracheal cyclopropane anesthesia the abdomen was opened through a long, left rectus incision. The liver was about three-fourths normal size, and the reduction in size was particularly marked in the left lobe, the lateral border of which just overlapped the medial border of the esophagus. The liver was a light gray, and its surfaces presented small scars. There were numerous thin adhesions between the liver and diaphragm. The spleen was about three times normal size, and its upper posterior surface was densely adherent to the anterior surface of the body of the stomach. The stomach was



Fig. 4.—Photograph of the fixed gross specimen. At the upper end a distinct rim of esophagus may be easily recognized, and a comparison of its dilated lumen may be made with narrowed lumen of the stomach. The walls of the stomach are thick with light fibrous tissue. At the lower end of the specimen normal duodenal mucosa is seen.



Fig. 5.



Fig. 6.

Fig. 5.—Microscopic section taken so as to include part of the esophageal wall and part of the gastric wall. The stratified squamous epithelium of the esophagus is seen as it joins with the gastric mucosa. Round cell infiltration may be seen extending to this level in the stomach.  
Fig. 6.—Photomicrograph showing intimal thickening and obliterative arteritis.

color, rough, and granular but without definite rugae. An irregular area of ulceration was present in the proximal portion about 4 mm. beyond the distal margin of the esophageal mucosa. This ulcer measured 13 mm. in its maximum diameter. It had sharp punched-out walls, and the edges, particularly at its distal margin, were undermined. It extended to a depth of 5 mm., and the wall of the stomach forming the base of the ulcer was 3 mm. thick. The base was irregular, rough, and of a dirty gray color, and it was covered by opaque, necrotic material. The remainder of the gastric mucosa presented many tiny areas of superficial ulceration and pin-point hemorrhages. The gastric wall gradually thinned out in the distal third to a 2 mm. thickness. The distal  $\frac{2}{3}$  cm. of the specimen was part of the duodenum. In this portion the mucosa was intact, light yellowish white in color, and markedly rugose.

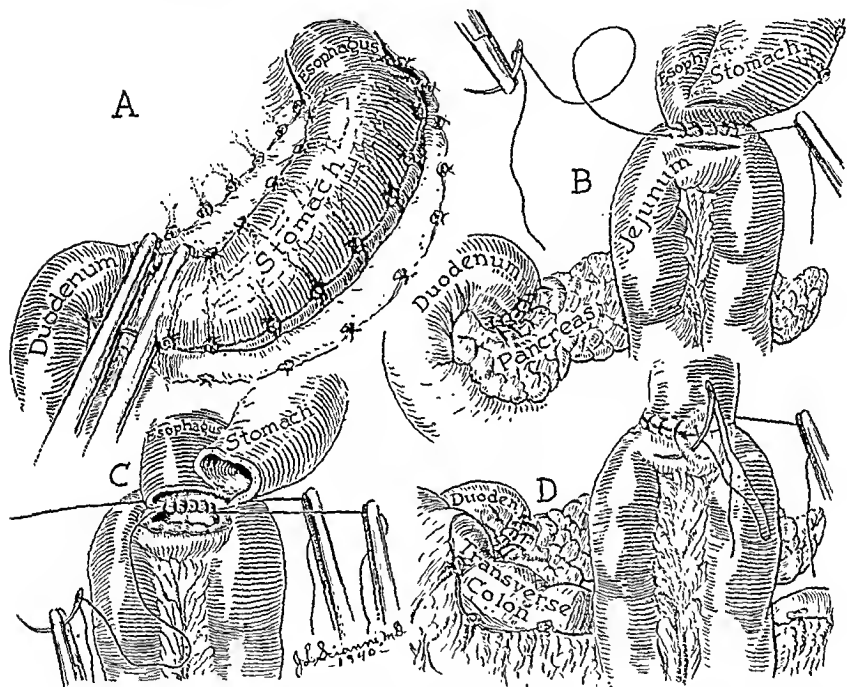


Fig. 3.—A, The greater and lesser curvatures have been freed, and clamps have been placed on the duodenum just distal to the pylorus. B, The duodenal stump has been closed, and the suture line has been reinforced with posterior peritoneum over the pancreas. The stomach has been turned upward and used for traction while the posterior approximation of the esophagus and the jejunum is made with a continuous catgut suture through the serous and muscular layers. The jejunum has been brought anterior to the transverse colon, and a point approximately 18 inches from the ligament of Treitz has been selected for anastomosis. C, The esophagus and jejunum have been opened and cleaned by suction, and the internal row of continuous catgut suture begun. Note that, not until the posterior internal row of sutures is finally placed, is the stomach completely severed at its proximal end. This is a most important step because, when the stomach is used for traction until the esophagus and jejunum are securely united by the two posterior rows of sutures, the most difficult technical handicaps are overcome. D, Here the stomach has been completely removed; the internal row of sutures has been completed anteriorly with a Connell suture; and the posterior approximating suture has been brought around and is being used as a continuous suture anteriorly to complete the anastomosis. A jejunojejunostomy is not done.

At the proximal end of the specimen the esophagus was dilated to a circumference of 6.5 cm. In the stomach the lumen was greatly narrowed and in the central portion measured only 1.5 cm.

The thick wall of the stomach was very firm and fibrous. The muscular layers could not be grossly identified.



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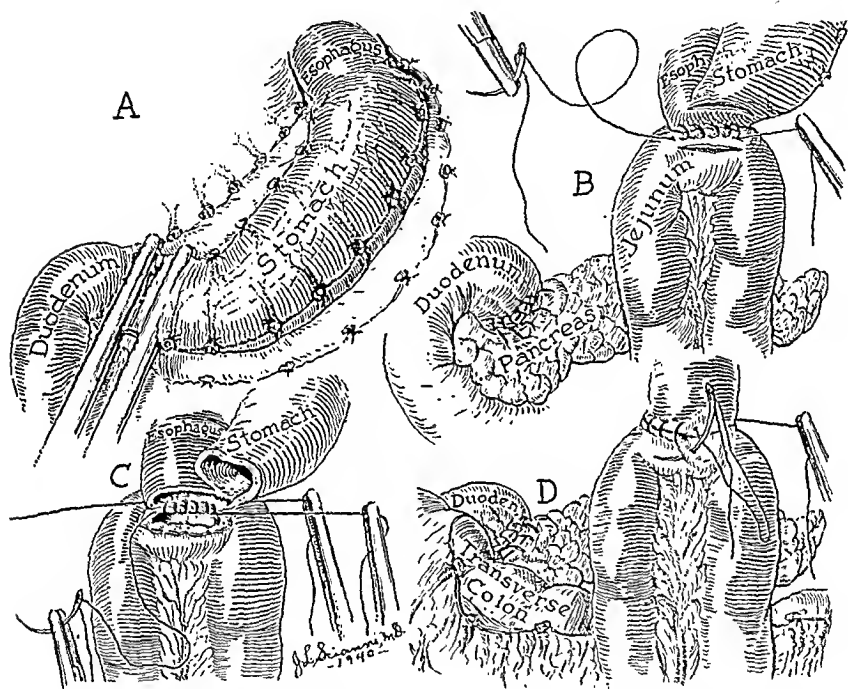


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The thick wall of the stomach was very firm and fibrous. The muscular layers could not be grossly identified.

*Postoperative Course.*—Convalescence was remarkably smooth and uneventful. Continuous suction siphonage of the jejunum was maintained for seventy-two hours, at which time the indwelling catheter was removed and small amounts of water were allowed by mouth at frequent intervals. There was a gradual increase in quality and quantity of food until the fourteenth postoperative day. At that time the patient was on a complete diet with the vegetables puréed and the meat ground and taking five small meals per day. (It is interesting that from the third postoperative day the patient complained of a ravishing hunger.)

The patient's gain in strength and weight was steady. He was discharged on Oct. 6, 1939, to the Out-Patient Department to receive antisyphilitic therapy. He has been very uncooperative, refusing all medical treatment and ignoring dietary instructions. He was last seen March 10, 1940, six months after operation, when his weight was 157 pounds, 41 pounds above the preoperative weight. He was eating a full diet, and his only precaution was the "chopping-up" of his food. Soon after he left the hospital, too rapid eating of food was followed by regurgitation, but at the present time the patient states that he can eat as much as anyone else and that he eats more often only because he is hungry all of the time.

His red blood cell count six months after operation was 3,750,000 per cubic millimeter with a hemoglobin value of 12.5 Gm. His red cell count has been consistently between 3,500,000 and 4,000,000 since operation.

TABLE I

CLINICAL FINDINGS	POOLE & FOSTER (1 CASE)	AUTHOR'S CASE
Age (years)	37	31
Sex	F	M
Race	W	C
Symptoms of gastric obstruction	Yes	Yes
Progressive weakness & wt. loss	Yes	Yes
Hematemesis	No	No
Duration of symptoms	12 mo.	4 mo.
Gastric HCl (fasting)	Free, 0; total, 4	Free, 0; total, 3
Wassermann reaction	Positive	Positive
Total R. B. C.	5,000,000	4,130,000
Hemoglobin	100%	12 Gm.
Palpable mass	No	No
Diffuse involvement of stomach	Yes	Yes
Total gastrectomy necessary	Yes	Yes
Recovery	Yes	Yes
Developed pernicious anemia	Yes	Too early

## COMMENT

Table I shows the remarkable similarity between Poole and Foster's case and mine. Eusterman<sup>3</sup> has described very accurately the clinical picture of syphilis of the stomach which these two cases typify. After reviewing the literature and reporting ninety-three additional cases from the Mayo Clinic, he stated that the clinical characteristics of syphilis of the stomach are "... the comparative youth of the patient (average age 34), the short duration of the symptoms in comparison to those of duodenal ulcer and the fact that they are more comparable to carcinoma than to ulcer, the high incidence of positive Wassermann reactions, the almost invariable absence of free hydrochloric acid in the gastric content, and its low concentration when present, and the characteristic filling defect, usually prepyloric and often accompanied by

*Microscopic.*—A section taken through the gastroesophageal juncture (Fig. 5) showed the squamous epithelium of the esophagus as it merged with the gastric mucosa. The wall in this portion of the stomach was greatly thickened by fibrous connective tissue which was most prominent as a layer between the circular and longitudinal layers of muscular tissue. This fibrous layer ended abruptly at the margin of the esophagus. There was an irregular, diffuse infiltration by round cells which was most prominent around or near small arteries. The same small blood vessels showed a rather marked degree of endarterial fibrous thickening (Fig. 6).

A section taken from the stomach wall showed a superficial area of ulceration of the mucosa with a dense exudate of fibrin and polymorphonuclear leucocytes on the surface. Beneath this in the submucosa there was a dense collection of chronic inflammatory cells, mainly plasma cells and lymphocytes but with some eosinophiles and polymorphonuclear cells. Some granulation tissue was present here at the base of the ulcer. Deeper in the submucosa the collections of chronic inflammatory cells were most prominent around or near small blood vessels. Some mild chronic inflammatory infiltration extended between muscle bundles in the muscular coat. There was some increase of connective tissue in the subserosa.



Fig. 7.



Fig. 8.

Fig. 7.—Another photomicrograph showing focal infiltration which some authors designate as miliary gummas. The cells are lymphocytes with an occasional plasma cell and eosinophile.

Fig. 8.—Rather marked perivascular infiltration with lymphocytes, plasma cells, and an occasional eosinophile.

In a section from a different portion of the wall formation of connective tissue was more marked. Focal (Fig. 7) and perivascular (Fig. 8) collections of lymphocytes were prominent, and intimal thickening of small arteries was present. Superficial small hemorrhages were present.

Several sections of tissue were studied by the Levaditi technique. There were occasional strands of tissue which took the silver stain, but these were so infrequent and so indefinite in detail that their identification as spirochetes seemed unjustifiable.

develop the function of holding a large portion of food which is one function of a stomach. It is also a sound physiologic principle to short-circuit bile and pancreatic secretions from as small a portion of the upper intestine as possible.

The maximal period of life following total gastrectomy, according to Walters,<sup>2</sup> has been four years and eight months. The question of how long it is possible for a patient whose stomach has been completely removed to live is as yet unsolved. Practically all total gastrectomies have been done for malignancies, and death in those upon whom operations have been successful has resulted from a recurrence of the malignancy. However, when total gastrectomy has been done for syphilis, the question of recurrence is eliminated and a more satisfactory answer to the question may be obtained. In a recent personal communication with Foster<sup>9</sup> he stated that the patient upon whom he did a total gastrectomy for syphilis<sup>1</sup> in 1926 was still living thirteen years and eight months after operation. She developed pernicious anemia four years after the operation, but the anemia has been satisfactorily controlled with the administration of ventriulin. This lends credence to the opinion that a person may maintain a surprisingly comfortable existence for an indefinite time without a stomach. Although my case has lived only seven and a half months to date, the ease with which nutrition is maintained is amazing, and it seems quite possible life and work may be carried on indefinitely particularly when regarded in the light of Poole and Foster's experience.

# SUMMARY

1. What is considered the second case of syphilis of the stomach necessitating total gastrectomy is reported in detail and compared with the only previously reported case.

2. The diagnostic criteria and the surgical indications for surgery of gastric syphilis are reviewed.

3. The technique of total gastrectomy is illustrated and the importance of omitting a jejunojejunostomy is stressed.

4. Life may be maintained successfully for an indefinite time when total gastrectomy has been done for a benign lesion even though a severe degree of anemia develops. The anemia may be satisfactorily controlled by medical means.

Since this case report was submitted to the publishers, there has been an interesting follow-up on the patient:

He was readmitted to the John Gaston Hospital Jan. 9, 1941, sixteen months after operation, with lobar pneumonia. Response to sulfathiazol was prompt and recovery rapid.

His red blood cell count was 4,500,000 and the value for hemoglobin was 13.2 Gm.

He was eating three meals a day. Each meal consisted of an unrestricted food selection, and he could eat as large a quantity at one meal as he had ever done. He

dilatation of the duodenal cap. . . .” He also emphasized that there is less emaciation, anemia, bleeding, and pain than one usually finds with other lesions producing such deformity as seen on the roentgenologic examination.

It is further noteworthy that the pathologic picture in Poole and Foster’s<sup>1</sup> case and the one reported here, although not conclusive when considered alone, is consistent with a diagnosis of syphilis and serves as confirmation of the clinical picture. The failure to find spirochetes in the tissue is disappointing, but it is a generally accepted fact that the demonstration of spirochetes in late syphilitic tissue is often impossible.

Ordinarily syphilis is considered a disease whose treatment is primarily medical. However, in the treatment of gastric syphilis surgery is frequently indicated. The differential diagnosis between syphilis and carcinoma, at times, is so difficult or impossible to make upon a clinical basis that resection of the lesion is indicated because it is the safest course to follow. Surgery is necessary in obstructing syphilitic lesions of the stomach because, as Beek<sup>4</sup> has pointed out, “. . . no antisymphilitic therapy will be able to cure a cicatricial contraction . . . operation is the cure of mechanical obstruction.” In accord with Beek are Allen,<sup>5</sup> LeWald,<sup>6</sup> and others. Graham,<sup>7</sup> in reviewing the literature, believes surgery for syphilis of the stomach is indicated when either bleeding, perforation, or obstruction is a complicating factor and concludes that resection of the pathologic tissue is the procedure of choice rather than some short-circuiting operation.

As antisymphilitic therapy may be relied upon to control the future advance of the disease, surgery’s singular purpose is the control of the pathologic process at the time of surgical attack. Total gastrectomy is indicated only when the entire stomach is so involved in cellular infiltration and scarring that nothing short of total gastrectomy will remove the pathology. In the case reported here, complete gastrectomy was never considered before the abdomen was opened. As may be seen in Fig. 1 the dilatation of the abdominal esophagus was easily misinterpreted as the gastric fundus, and I felt that a subtotal gastrectomy would be relatively easy. However, when the pathology was actually seen, the total extirpation of the stomach was necessitated, for only after its removal was it mechanically possible to do an esophagojejunostomy.

The total gastrectomy as illustrated in Fig. 3A, B, C, and D was made simpler than usual by the elongation and dilatation of abdominal esophagus.

An enteroenterostomy between the loops of the jejunum was not done. Lahey<sup>8</sup> has pointed out that this procedure is not only unnecessary but undesirable in the majority of cases. If the anastomosis between the esophagus and jejunum is free and mobile, the proximal loop will empty satisfactorily. Furthermore, the proximal loop may dilate and at least

# EPILOIA

## REPORT OF CASES

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*(From the Department of Surgery of the College of Medicine, University of Cincinnati, and the Cincinnati General Hospital)*

EPILOIA is a clinical syndrome characterized usually by mental deterioration, epilepsy, adenoma sebaceum of the skin, and tuberous sclerosis of the brain. Other features inconstantly associated with the syndrome are benign tumors of the liver, spleen, kidney, heart, gastroenteric tract, retina, lung, thyroid, thymus, uterus, urinary bladder, and nail beds.

Sherlock<sup>1</sup> in 1911 coined the name epiloia for this remarkable clinical and pathologic entity. In England and in Europe approximately 1 per cent of the institutionalized epileptics and mental defectives suffer from this disease. In the United States the incidence of epiloia is reported to be but one-tenth as frequent. Hopwood,<sup>2</sup> for instance, found 5 cases of epiloia from a total of 4,000 records (0.1 per cent) at the Institution for Feeble-minded, Orient, Ohio. Epiloia is described by Sherlock as a heredofamilial degeneration, and a family psychopathic history is sometimes obtainable. The occurrence of epiloia in one family through three generations has been reported by Kirpiznik<sup>3</sup> and in 5 of 9 siblings by Bouwdijk, Bastiaanse, and Landsteiner.<sup>4</sup> Fabing<sup>5</sup> reported the presence of epiloia in both of identical twins and, especially because of the mirror-image position of some of the skin and neurological lesions in his patients, concluded that the disease resulted from a defect in the zygote in its early life and that it was probably a truly hereditary (genotypical) disorder. Cockayne<sup>6</sup> states that epiloia is a dominant characteristic which appears to be very incomplete so that heterozygotes are sometimes indistinguishable from normal individuals. This would account for the number of isolated cases.

It is difficult to describe the clinical manifestations of epiloia due to the extreme variability in the symptomatology the individual patient may present. In general, however, the onset of the disease is manifest in infancy or early childhood. Mental deficiency is usually marked and developmental delay consequently is readily recognizable. Idiocy is a common finding. Epileptic seizures begin at an early age, but the type of attack is difficult to predict. One patient died in her first epileptic seizure at the age of 21 years. The facial lesions (adenoma sebaceum) become apparent within the first decade and abrupt development at the

had had no regurgitation of food for six months. His weight was 165 pounds, which represented a 50 pound gain since his operation.

X-ray studies revealed that the proximal loop of the jejunum had dilated to about two times normal size and was emptying normally.

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gers and toes. The size may vary from that of the small filiform tumor to the golf ball-sized tumor which we noted in two of the cases in our series of cases. In some instances the nail-bed tumors cause pain and discomfort and this is particularly true if secondary infection and hemorrhage occur. Microscopically the tumors are composed of a surface layer of heavily keratinized, stratified squamous epithelium. The underlying layer consists of a well-differentiated and somewhat hyalinized fibrous connective tissue in which an occasional giant cell can be seen. The nails after a period of time undergo degenerative changes and become grooved. Chronic paronychia are not uncommon. Surgical removal is indicated if the tumors are giving rise to pain or discomfort or if hemorrhage and secondary infection have proved troublesome. In our experience the tumors do not tend to recur following complete surgical removal.

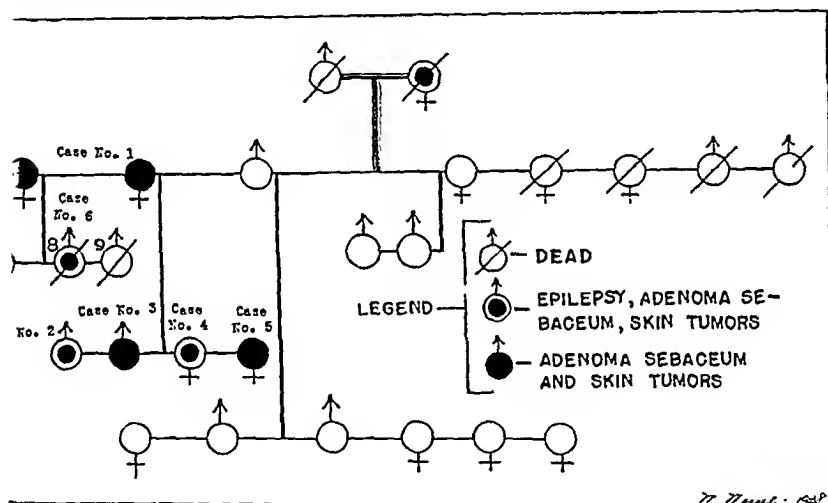


Fig. 1.—Genealogy of the epiloia family. Three generations are shown. The relation in the family tree of the individual cases presented in this paper is indicated.

#### CASE REPORTS

Six members of one family in whom the diagnosis of epiloia has been established have come under our direct observation. Each of the six cases that we studied exhibited epiloia in more or less complete form. Autopsy examination was performed in the seventh case. An attempt was made to determine the extent of the involvement by this disease in the family through three generations. Data relative to dead or absent members of the family were obtained by the careful examination of photographs and by history obtained from Mrs. H., the most intelligent member of the family at our disposal. Follow-up studies for a period of over two years have been carried out and observations relative to the progression of the disease are given with each case history.

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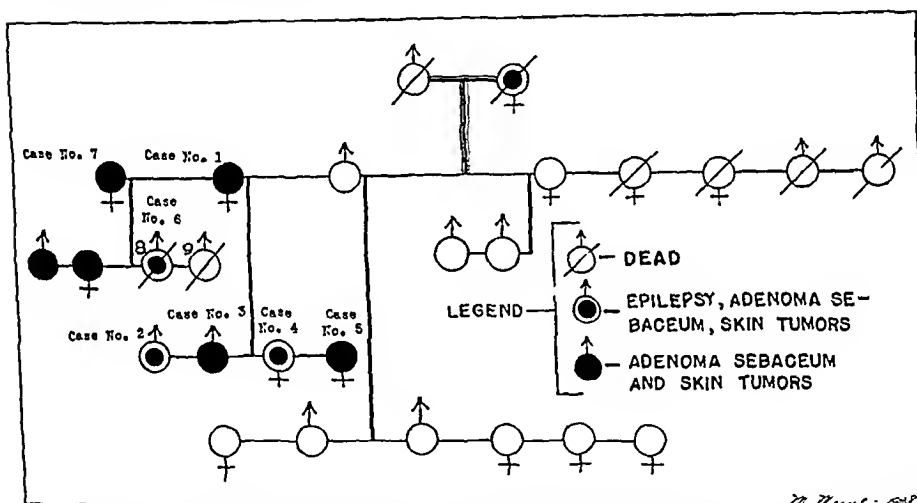


Fig. 1.—Genealogy of the epiloma family. Three generations are shown. The relative position in the family tree of the individual cases presented in this paper is indicated.

#### CASE REPORTS

Six members of one family in whom the diagnosis of epiloma has been established have come under our direct observation. Each of the six cases that we studied exhibited epiloma in more or less complete form. Post-mortem examination was performed in the seventh case. An attempt was made to determine the extent of the involvement by this disease in the family through three generations. Data relative to dead or absent members of the family were obtained by the careful examination of photographs and by history obtained from Mrs. H., the most intelligent member of the family at our disposal. Follow-up studies for a period of over two years have been carried out and observations relative to the progression of the disease are given with each case history.

time of puberty is the usual sequence. Death occurs at an early age as a rule, but the mortality is in direct relationship to the extent of the mental deficiency, the development of the brain lesions, and the possible presence of visceral neoplasms. Incomplete or abortive forms of epiloia with the utmost variation in clinical findings exist and one must keep this fact constantly in mind in diagnosis.

Bourneville<sup>7</sup> in 1880 first described tuberous sclerosis or the main component of Sherlock's epiloia syndrome as a purely pathologic entity found at autopsy in young patients who had shown mental deficiency and epilepsy during life. The term "tuberous" Bourneville used to indicate the potato-like appearance of the sclerotic patches scattered throughout the cerebral cortex and ventricles of the brain. He regarded the cutaneous lesions (adenoma sebaceum) and the visceral neoplasms that he noted also in such patients as coincidental. The pathologic background of the disease has remained uncertain to the present day. Some authors favor a neoplastic process, some a vascular process, and still others maintain that it is a developmental anomaly. The brain lesions are found in the cortex and immediately beneath the ependyma projecting into the lateral ventricles. The tumors are present in multiple areas and the potato-like appearance is unmistakable. Microscopically, these tumors are composed of a neuroglial proliferation and remarkably large giant cells of glial origin (riesenzellen). Degenerative changes are manifest in many portions of the tumors.

The skin lesions of epiloia, the so-called adenoma sebaceum, were described and named by Pringle<sup>8</sup> in 1890. Adenoma sebaceum is a nodular eruption of red to brown color distributed over the face. The rash originates in the nasolabial folds and extends over the cheeks in butterfly pattern. Three types of adenoma sebaceum occur. The Pringle type of rash is red in color; the Balzer type is composed of pale nodules; and the third, the Hallopeau-Leredde type, is characterized by hard and wartlike nodules. Microscopically, adenoma sebaceum consists in a benign hyperplasia of the sebaceous glands. The red coloration of the Pringle type results from associated telangiectases. The hardness of the Hallopeau-Leredde type is due to excessive fibrous tissue proliferation.

Still other cutaneous lesions have been distinguished by various authors. Critchley and Earl<sup>9</sup> call particular attention to fibromas scattered over the trunk. Nevi, pigmentary disorders, vitiligo, hypertrichosis, cutaneous horns, white hair in the eyebrows, and pigmented and hairy moles are found in some instances. Nail-bed tumors in association with the syndrome of epiloia have been reported by Reitmann,<sup>10</sup> Hintz,<sup>11</sup> Fuhs,<sup>12</sup> Busch,<sup>13</sup> Elliot,<sup>14</sup> James,<sup>15</sup> and MacKenna.<sup>16</sup> These latter unusual but quite characteristic tumors were present in the entire series of cases presented here and are worthy of special consideration. They are filiform papillomas or fibromas and are located at the nail cutaneous juncture on

This patient now has been followed over a period of two years. No change in the mental status has occurred. The nail bed tumors have not recurred. There is still no evidence of visceral neoplasm (Figs. 2 and 3).

CASE 2.—L. H. was a white male, 22 years of age, the oldest son of Mrs. M. H. (Case 1). According to the history obtained from his mother, he had been subject to epileptic attacks of grand mal type since 1 year old. This boy showed marked mental deterioration. He was an inmate of the State Home for Epileptics



Fig. 2.—Case 1, 1938. The facial lesion of epiloia, adenoma sebaceum, is well illustrated.

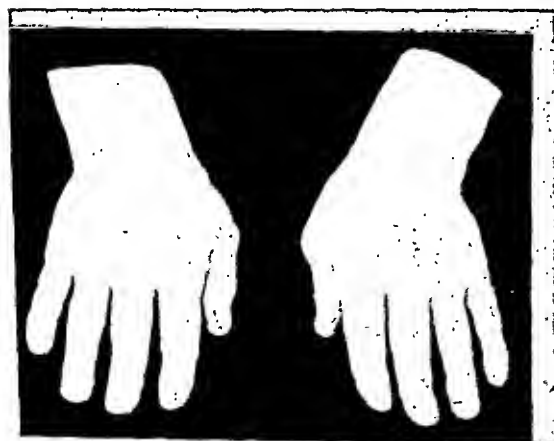


Fig. 3.—Case 1. The nail-bed lesions of the fingers and toes which are present in the entire series of cases are best illustrated in this epiloia patient.

at Gallipolis, Ohio, and he was able to perform simple manual tasks. Physical examination revealed a well-developed adenoma sebaceum of the Pringle type spread over the face in typical butterfly arrangement. There were numerous moles and wartlike growths distributed over the neck and trunk. The nails of the fingers and toes were grooved, and there were a small, hard tumor present in the nail bed of

The mother of the patients in Cases 1 and 7 and the grandmother of the patients in Cases 2, 3, 4, 5, and 6 died at the age of 33 years with pneumonia. According to her daughter, Mrs. H. (Case 1), she had petit mal attacks which began at the age of 18 years and had facial lesions similar to her own, as well as nail-bed tumors (Fig. 1).

CASE 1.—Mrs. M. H. (History No. 80902, Cincinnati General Hospital), a white female, 43 years of age, came to the Tumor Clinic of the Out-Patient Dispensary of the Cincinnati General Hospital in October, 1937, with the complaint of painful tumors on the fingers and toes. She had noted the presence of a small hard tumor under the nail of the third finger of the right hand at the age of 16 years. Similar growths had appeared at varying intervals since that time on the other fingers and toes. The tumors increased very slowly in size. This was particularly true of the growths on the toes, which were irritated by her shoes and which bled frequently. Infected ingrown nails likewise occurred at frequent intervals. Also, at the age of 16 years, or perhaps a short time later, the patient noted a papular eruption about the nose and face, which, while always present, seemed to have periods of exacerbation and remission. At the age of 34 years, however, she realized that the eruption about the face was definitely more pronounced and more extensive. No therapy for this condition was attempted. At the age of 38 years the tumors on the toes attained considerable proportions, and she had difficulty in wearing shoes and in walking. Hemorrhage from these tumors was severe on several occasions, and the patient "pared" the growths and applied iodine several times with transient relief of her symptoms. Past history was entirely negative. Her health had always been good. There was no history of headaches, vertigo, convulsions, or other type of neurological involvement. Her childhood and puberty apparently were uneventful. She had gone through the second year of high school and stated that she always got along well in school. She had been married twenty-four years and had four children. Her husband was living and well, and there was no apparent familial discord. She had many friends and adjusted herself well socially.

Physical examination was entirely negative except for the face, fingers, and toes. Height was 61 inches and weight, 137 pounds. On the face and nose there was a well-developed adenoma sebaceum of the Pringle type spread in typical butterfly pattern over the nasolabial folds and cheeks with one large discrete papillomatous growth at the base of the nose. Discrete, hard, gray to pink colored tumor masses were present at the nail cutaneous juncture of all the fingers and the toes. These tumors varied in size from that of a pea to a size slightly less than that of a golf ball. The larger tumors were on the toes and secondary infection in these neoplasms was the evident cause of her symptoms. The nails themselves were grooved. Neurological examination and spinal puncture were negative. According to the Stanford-Binet test, this patient had a mental age of 13 years 6 months with a resultant intelligence quotient of 84. She was, therefore, close to being of average intelligence. The opinion of the examiner was that she evidenced no deterioration in her mental abilities. Roentgenographic studies of the head, chest, and abdomen, including pyelograms, failed to reveal the presence of a visceral tumor.

The tumors on the toes were excised after secondary infection had cleared up. Microscopic examination of the neoplasms revealed a very thick keratinized surface layer of stratified squamous epithelium overlying a subcutaneous layer of cellular fibrous connective tissue. Several of the tumors prior to surgery were treated with radium and x-ray to determine radiation sensitivity. No response to this treatment was obtained.

idiot and had had epileptic seizures of grand mal type since the age of 5 months. She also was an inmate of the State Home for Epileptics at Gallipolis, Ohio. She was totally unable to care for herself and was animal-like in appearance. She mumbled constantly to herself in an indistinguishable tone of voice as she rocked herself back and forth with accompanying athetoid movements of the forearms and hands. Adenoma sebaceum was present but poorly developed. The nails were grooved with a minute nail-bed tumor on the fifth finger of the right hand. There were numerous keloid scars scattered over the body. Neurological examination when first made in 1937 was completely negative except for the athetoid movements. Re-examination in January, 1940, revealed several findings: slight weakness of the right side of the face, deep reflexes on the right more active than on the left, and the right side more spastic generally than the left. She constantly tended to assume a scissors position of the legs. In 1931 following study at the Cincinnati General Hospital and the Jewish Hospital of Cincinnati, an exploratory craniotomy was performed. Diffuse sclerotic patches were found scattered over the cortex. The diagnosis of an inoperable brain tumor, probably a glioma, was made. X-ray studies are not obtainable.

CASE 5.—J. H. (History No. 52153, Cincinnati General Hospital), was a white female, 14 years of age, the fourth child of Mrs. M. H. (Case 1). She was of average intelligence and had reached the first year of high school. Adenoma sebaceum was detectable on the face. There were small cutaneous nevi on the abdomen and extremities. Nail-bed tumors were present on the fifth finger of the right hand and the fourth toe of the left foot. Neurological examination was negative. There was no history of epilepsy. X-ray studies were entirely negative.

CASE 6.—L. W. was the third child of the sister of Mrs. M. H. (Case 1) and the first cousin of the patients in Cases 2, 3, 4, and 5. He was subject to epileptic seizures of grand mal type from infancy. He died in 1930 at the age of 5 years. At the time of death he was under the care of a private physician who made the diagnosis of a brain tumor. No further record was available. An autopsy was performed, and the diagnosis of a brain tumor of a glial type was made. The post-mortem examination was limited to the head. Fortunately the brain was saved. In a pathologic report dated June 14, 1930, Dr. Pearl Zeek, of the Pathologic Department of the Cincinnati General Hospital, made the following observations: "The specimen consists of a brain removed from a child about 5 years old. The brain tissue is extremely soft and cannot be completely examined until further fixation has taken place. However, there is marked asymmetry of the two cerebral hemispheres and on a partial horizontal incision beginning at the frontal pole a large soft mass resembling neoplastic tissue rolled out of the lateral ventricle. This tissue shows yellowish pigmentation in places and is extensively necrotic and blood stained. There is no evidence of meningitis. Diagnosis: Brain tumor, possibly a glioma." Microscopic study was not done at the time.

This brain, which had been preserved in Kaiserling's solution, was re-examined by Dr. Charles Aring, of the Neuropathology Department, University of Cincinnati, who in 1938 made the following report: "The entire brain is of soft consistency and one cannot make an accurate description of the cortex as the sulci have been flattened and softened, due to many years of storage. Through and through sections have been made of the cerebral hemispheres. The lateral ventricles are tremendously dilated and filled with tumor masses of cheesy consistency. These masses are now 2 to 8 cm. in length and 1 to 5 cm. in breadth and width. Microscopic examination shows these tumors to be composed of cells of large size and rather uniform outline. Blood vessels are numerous. The stroma of the tumor is marked and is probably made up of the processes of the cells. The cells vary in size and

the third finger of the left hand and numerous tumors of the nail beds on all the toes. These latter neoplasms were quite small in size and never had occasioned the patient any difficulty by their presence.

Neurological examination when first made in 1937 gave no positive findings with the exception of a marked tache cerebrale and a nonsustained fibrillary nystagmus on lateral fixation. Within the previous two years he had developed a left facial hemiatrophy and ptosis of the lower left eyelid. The significance of these neurological findings was not determinable. He had a mental age of 7.6 years with an intelligence quotient of 49. His epileptic attacks occurred for the most part during the night. There has been little or no progression in the size of the nail bed tumors within the two-year period that he has been under our observation (Fig. 4).

CASE 3.—R. H. (History No. 83453, Cincinnati General Hospital), was a white male, 21 years of age, the second son chronologically of Mrs. M. H. (Case 1). The past history was entirely negative except that apparently he was subject to some type of epileptic seizures during infancy. He attended a school for the mentally retarded, and at the age of 16 years dropped out, having reached the



Fig. 4.—Case 2. The nail-bed tumors of this epiloia patient are well developed.

fifth grade. According to the Stanford-Binet test in 1937, he had a mental age of 8 years 10 months, with a resultant intelligence quotient of 55. He was, therefore, definitely mentally retarded. He was tested at the Vocation Bureau on Jun. 6, 1926, when he was 7 years old. His mental age then was 4 years 10 months, and his intelligence quotient was 69. He was tested again at the Vocation Bureau on Sept. 11, 1933, when he was 14 years 8 months old. At that time he had a mental age of 8 years 10 months with intelligence quotient of 60.

Physical examination revealed a stupid appearing individual of 21 years. A well-developed adenoma sebaceum of the Pringle type was present on the face. Multiple papillomatous growths were noted on the neck and shoulders. Café au lait patches were present on the face, thorax, and abdomen. Nail-bed tumors of small size were present on all the toes and the third and fifth fingers of the right hand. Repeated neurological examinations of this patient were negative. The nail bed tumors were excised surgically and no recurrence was detectable. Microscopically these tumors had the same structure as those removed from the patient in Case 1. X-ray studies of this patient were entirely negative.

CASE 4.—V. H. (History No. 5030, Cincinnati General Hospital), was a white female, 16 years of age, the third child of Mrs. M. H. (Case 1). She was an

there are veritable nests of giant cells. There are patchy areas of demyelination in the vicinity of the nests of cells in the white matter of the cerebral cortex. In some places this demyelination is present in an entire gyrus. . . . Diagnosis: Tuberous sclerosis." (Figs. 5 and 6.)

CASE 7.—Mrs. W. was a 47-year-old white female, the mother of L. W. (Case 6) and the sister of Mrs. M. H. (Case 1). She was unwilling to submit to examination, photography, or other type of special workup. She was subject to petit mal seizures which she referred to as "trembling spells." A well-developed adenoma sebaceum of the Pringle type was present on the face and nose. Nail-bed tumors which varied from filiform papilloma to golf ball-sized neoplasms were present on the fingers and toes. Secondary infection had occurred in several of the tumors of the toes. Hemorrhage from the tumors had occurred on numerous occasions. The nails themselves were grooved, and chronic paronychias were distinguishable.

#### COMMENT

Although the mother of Cases 1 and 7 (the grandmother of Cases 2 to 6) was not examined clinically, the history of epileptic seizures, adenoma sebaceum, and nail-bed tumors in this woman make the diagnosis of epiloia in her case a valid presumption. If this is granted, the foregoing study reveals the direct passage of the disease through three generations.

The study discloses that, if the epiloia patient lives through puberty and is capable of mating, transmission of the disease is possible. Undoubtedly the reason for so few examples of this type of transmission in the literature lies in the fact that the average patient with epiloia is so mentally and physically incapacitated at puberty that marriage and mating cannot occur.

Study of the family tree discloses that one daughter (Case 1) of the original epiloia patient transmitted the disease in all its intensity to all four of her children who lived to puberty; whereas, the other daughter (Case 7), who shows signs of the disease, apparently did not pass it on to her two older children. This reveals the undoubtedly complex nature of the transmission. In the instance of the other two children of the original epiloia patient who had issue, there is no evidence of the disease. It is not found in their children as well. This suggests that the disease is not a recessive characteristic but rather a dominant characteristic which tends to be incomplete, as Cockayne<sup>6</sup> contends.

The nail-bed tumors, an uncommon accompaniment of the epiloia syndrome, are worthy of notice because of their consistent presence throughout the entire series of cases. The presumption here is that epiloia is transmitted even in its minute details.

Last, the direct transmission of the disease from parent to offspring through three generations, as presented by this study as well as that of Kirpiznik,<sup>2</sup> proves that the syndrome is truly hereditary, i.e., genotypical, as suggested by Fabing<sup>5</sup> in his study of the disease in identical twins.

some of them reach enormous proportions. The nuclei stain deeply, are irregularly shaped, and are placed at the periphery of the cell. Many of the cells are multinucleated. No mitoses are seen.

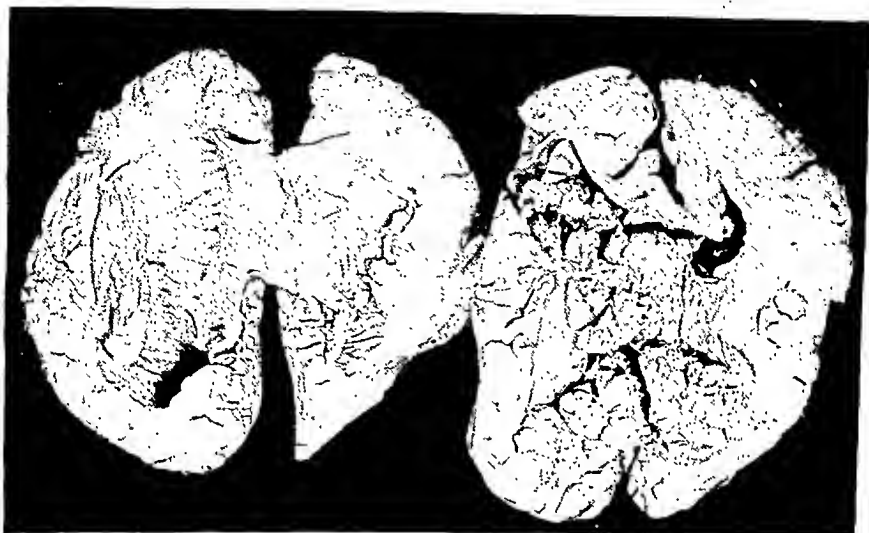


Fig. 5.—Case 6. Hemisection of the brain illustrating the tuberous masses filling the ventricles as described by Bourneville.

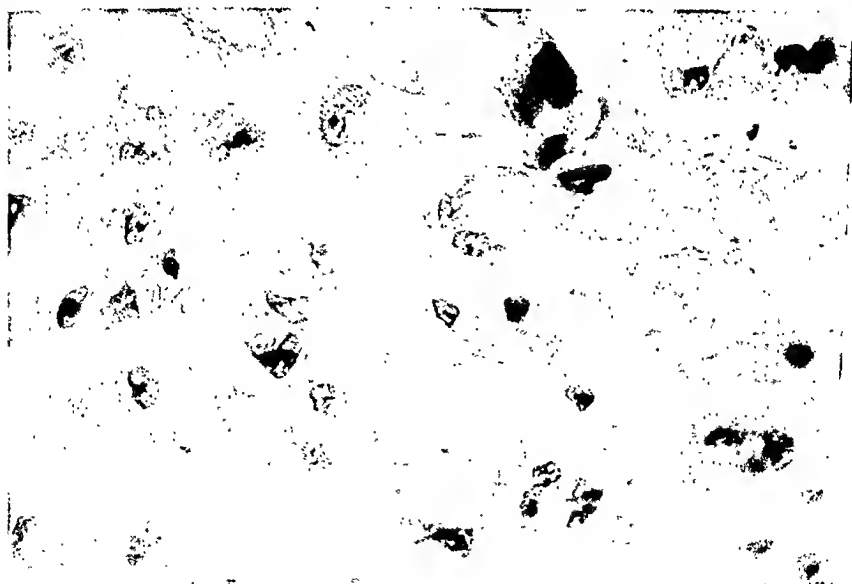


Fig. 6.—Case 6. High-power view of section through brain tumor. The giant cells, characteristic of tuberous sclerosis, are well illustrated.

“Study of sections taken from the cerebral cortex shows complete cytoarchitectonic disorganization. Large cells which appear similar to those described previously are scattered through the widened cortical layers. In some locations

there are veritable nests of giant cells. There are patchy areas of demyelination in the vicinity of the nests of cells in the white matter of the cerebral cortex. In some places this demyelination is present in an entire gyrus. . . . Diagnosis: Tuberous sclerosis." (Figs. 5 and 6.)

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## SUMMARY

1. The syndrome of epiloia is described.
2. A family tree is outlined in which the disease seemed to appear in three generations.
3. Seven case histories are outlined.
4. The presence of nail-bed tumors, an unusual accompaniment of the syndrome, is noted throughout the group.
5. The contention is advanced that, if the patient with epiloia lives beyond puberty with reasonably good mental and physical health, he or she may transmit the disease to the next generation.
6. The study is offered as proof of the truly hereditary or genotypical transmission of the disease.

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## A SYSTEM OF SURGICAL FOLLOW-UP AND RECORD KEEPING

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*(From the Department of Surgery, Duke University School of Medicine)*

TO LOCATE, assemble, and peruse a large number of hospital records is such a laborious duty that few have the time or patience necessary for such a task. As a result, every hospital record room contains a wealth of clinical data which lie hopelessly buried beneath the technical difficulties of bringing them to light. In order to facilitate the collection of clinical data from the records of hospital admissions and return visits and, at the same time, to furnish a system of follow-up on all hospital cases, a procedure has been established on the Surgical Service of the Duke Hospital which has proved itself to be quite satisfactory.

The system of follow-up and record keeping is set up about one file which contains a follow-up sheet (Fig. 1) for each patient operated upon. On this sheet is recorded a brief abstract of all the pertinent findings in the hospital course. On this sheet also is subsequently recorded an abstract of each follow-up visit. These sheets filed chronologically according to operation bring together in one folder all the hospital and follow-up data on each group of operative cases. With them the department is able to summon each group of cases systematically for follow-up. In addition, the department is able to give statistical information easily and quickly at any time concerning the hospital record, the immediate hospital mortality, and the follow-up results in each group of cases operated upon.

The follow-up clinic is staffed by one full-time secretary. Clinic data are accumulated in one file, containing a follow-up sheet for each patient operated upon, and one book in which are compiled by year and by total hospital experience the immediate hospital mortality and the follow-up results on each group of cases.

The follow-up sheet, which is filled out for each patient, is an eight and one-half by eleven inch sheet of heavy twenty-eight pound ledger paper on which a basic form for the follow-up clinic is printed, as in Fig. 1. In the space for clinical abstract a brief account of the history, physical examination, laboratory findings, operative findings, and post-operative course is recorded. In certain of the more frequent conditions which are of especial interest a special form is printed in the space for clinical abstract (Fig. 2). Such forms are used for diseases of the

appendix, biliary tract, breast, thyroid, stomach, and colon and for thoraeoplasties. These forms are checked at history meetings, and, being filled out in full, they insure complete recording of all pertinent data.

The follow-up sheet is filled in by the clinical clerk or by the intern on the ward. When the patient is discharged from the hospital, his record passes over the resident surgeon's desk. Here the hospital record is diagnosed and the follow-up sheet is checked to see that it is complete and then is removed from the record. The follow-up sheet is then coded according to operation and sent to the follow-up clinic for filing, which is done according to a classification of the operations done by the general surgical staff.

Form No. 5172		SURGICAL FOLLOW UP CLINIC		Date
Name _____	Family Doctor _____			
Address _____	Address _____			
Clinical Abstract: _____		MF WC SMWDS		Name
				Age
				Operation
Diagnosis: _____				Operator
Previous Operations in this Hospital: _____				Assist
S. Path No. _____	Report: _____			
Complications: _____				
Result: _____				
When to return _____				
If dead was autopsy obtained _____				
Follow Up Notes: _____				

Fig. 1.—The basic form for the follow-up sheet. In the space for clinical abstract pertinent facts in the history, physical examination, laboratory findings, operative findings, and postoperative course are recorded under separate paragraphs.

When each patient returns for check-up examination, and on every subsequent follow-up visit, notes on his condition are transcribed onto the follow-up sheet. Information on the follow-up sheet is thus kept constantly up to date. These data are transferred to the follow-up sheet by the department secretary who inspects the unit history of every patient making a return visit to the hospital each day. She keeps out those cases treated on the surgical service and abstracts the note made in the clinic on the follow-up sheet.

When the follow-up department was first organized in 1937, it did not contain the operations of the preceding seven years dating back to the opening of the hospital in July, 1930. A sheet for each of these

SURGICAL FOLLOW UP CLINIC										Date
Name _____ Family Doctor _____					Address _____					
MR. MC SWEDS										No
<b>Chief Complaint:</b> GALL BLADDER AND DUCTS History: No. pregnancies _____ Duration of symptoms _____ Flatulency _____ Indigestion _____ Foods which disagree _____ Character and location of pain _____ Biliary colic _____ Frequency of colic _____ Last attack colic _____ When jaundiced in past _____ Duration of jaundice now _____ Chills in past _____ Date last chill _____ Acute cholecystitis in past _____ Operations on biliary tract _____ Nausea severe _____										
Phys. Exam. on admission: T _____ P _____ R _____ WBC _____ BP _____ Ht _____ Wt _____ Jaundice _____ Van den Bergh _____ Bile in stool _____ in urine _____ Abd. signs _____ X-ray findings _____ Preop. diag. _____ Days in hosp. before op. _____										Name
<b>Operation:</b> Incision _____ CB culture _____ Condition of GB: (circle) Normal; stones; thickened; contracted; distended; gangrenous; carcinoma; other condition _____ Condition of cystic duct: Normal; dilated; occluded by stone _____ Condition of common duct: Dilated; stone; mud; stricture; neoplasm _____ Was common duct exposed _____ Finding _____ Pancreas indurated _____ Other op. procedures _____										
<b>Postoperative course:</b> Biliary drainage _____ Biliary colic _____ Highest P. O. temp. _____ Days until temp. normal _____ P. O. jaundice _____ If common duct was drained no. days until tube removed _____ Days until bile drainage stopped _____ Days until jaundice disappeared _____ Days in hospital after operation _____ If dead cause of death _____										Age
<b>Diagnosis:</b> _____										
<b>Previous Operations in this Hospital:</b> _____										Operation
<b>S. Path. No. _____ Report _____</b>										
<b>Complications:</b> _____										
<b>Result:</b> _____ When to return _____										
<b>Follow Up Notes:</b> _____ If dead was autopsy obtained _____										
										Operator

Fig. 2.—The special form of the follow-up sheet used for gall bladder operations. Special forms have also been prepared for diseases of the appendix, breast, thyroid, stomach, and colon and for thoracoplasties.

operations was prepared, however, from the data available in the files of the operating room. Information available from this source was sufficient only to fill in the data along the vertical column on the right side of each follow-up sheet (Fig. 1). To complete the sheet, it was necessary to obtain the unit history of each case and record the pertinent data. This work has been done by a group of students employed under the NYA. In some groups of cases no effort has been made to fill out the clinical abstract. In those of interest for follow-up purposes, however, the entire follow-up sheet has been completed for all the early cases.

#### METHOD OF FOLLOW-UP

A specific month each year is set aside in which to follow each group of cases. Thus, stomach operations are followed in October, colon cases in November, thyroid cases in December, gall bladder cases in January, appendix cases in February, hernia cases in March, rectal cases in April, chest cases in May, breast cases in June, and miscellaneous conditions in July, August, and September. All cases with malignant tumors, peptic ulcers, or pulmonary tuberculosis are followed yearly. Remaining cases with a few exceptions are followed yearly for three years and then every five years.

A form letter is prepared for each group of cases followed. The following is a form letter used in follow-up of gall bladder operations. Similar forms are prepared for each operative procedure.

We are very much interested in knowing how you have been getting along since your gall bladder operation at the Duke Hospital, and should appreciate it very much if you would answer the questions below. The answers may be written in the space following each question and the letter returned to us in the enclosed envelope, which requires no stamp.

1. Do you believe yourself to be cured, improved or unimproved by the operation?
2. Have you had any gall bladder colic since operation? If so, when and how often?
3. Have you been jaundiced since the operation? If so, when and how often?
4. Do you have any indigestion? Describe it.
5. Are you less constipated, more constipated, or has there been no change in bowel movements since operation?
6. If you have moved, what is your new address?

If you feel that your symptoms have not been relieved, we would like to have you return to the Clinic for re-examination. The enclosed card, presented at the Clinic entrance any afternoon, except Saturday and Sunday, at 1:00 P.M., will entitle you to examination without charge, if you come before the date stamped on the card.

Looking forward to hearing from you promptly, I am,

Sincerely yours,

Surgical Follow Up Clinic.

This form letter is mailed to each patient in the group, being sent by first class mail. If the letter is not answered and is not returned, it is assumed that it has been received but ignored and a second similar letter is sent ten days later. If the second letter is ignored, a third is sent ten days after the second. If no answer is received from these letters or if the first letter has been returned marked unknown, moved, etc., letters are written to relatives, the family doctor, or the local welfare agency in an effort to locate the patient. Each letter contains a business reply envelop which requires no stamp which the patient is asked to use in returning answers to the questionnaire. Each letter also contains a card admitting the patient to the clinic without charge for check-up examination, if the visit is made in the month specified for the follow-up.

It has been our experience that 45 per cent of patients will respond to the first letter, another 23 per cent to the second, and 14 per cent to the third. Letters to the family doctors, relatives or welfare agencies are successful in locating another 10 per cent. In about 7 per cent of our cases no follow-up has been possible and we have had to record such patients as lost.

The problem involved in follow-up at the Duke Hospital is complicated by the fact that the hospital serves a rural community whose average patient comes a distance of seventy-seven miles. Only 22 per cent of patients come from Durham. Of the patients admitted, 86.8 per cent are charity or part pay patients and 16 per cent are negroes who shift their residence frequently. For economic reasons, it is frequently difficult for our patients to present themselves at the clinic for re-examination. If such is the case in patients whose symptoms continue, the patient's local doctor is asked to submit data concerning him.

Under this system, we have been able to obtain a satisfactory follow-up in 92.5 per cent of our large operative cases (Table I) operated upon from the time the hospital opened in 1930 until the present. A follow-up is much more successful if patients are followed promptly and regularly. As shown in Table II, we have been unsuccessful in tracing 18 per cent of our patients operated upon the first year the hospital was open, no effort being made to locate these patients until eight years had

TABLE I  
NUMBER OF PATIENTS FOLLOWED

OPERATION	NO. PATIENTS DISCHARGED	NO. PATIENTS FOLLOWED	PERCENTAGE FOLLOWED
Stomach operations	209	194	92.8
Colon operations	103	94	91.2
Radical mastectomy	173	163	94.2
Thyroid operations	396	367	92.6
Gall bladder operations	405	371	91.3
Total	1,286	1,189	92.5

TABLE II

PERCENTAGE OF PATIENTS LOST TO FOLLOW-UP IN 1940  
TABULATED BY YEAR OF OPERATION

YEAR	PERCENTAGE OF PATIENTS LOST TO FOLLOW-UP
1930-31	18.0
1931-32	13.0
1932-33	16.3
1933-34	10.1
1934-35	10.0
1935-36	5.4
1936-37	7.6
1937-38	3.2
1938-39	0.5

elapsed following their discharge from the hospital. On the other hand, in the group operated upon in the past three years since the follow-up clinic has been in existence only 3.7 per cent of a total of 608 patients have been lost.

Tabulation of immediate hospital mortalities is compiled yearly and for the total hospital experience for each group of cases. These data are filled in on a special form and bound in a loose-leaf book. In the same book are also tabulated each year the follow-up results on each group of cases.

Annual reports are furnished the head of the surgical department giving the hospital mortality for the year and for the total hospital experience and the follow-up results on each group of cases operated upon on the general surgical service. These results are discussed in staff conference. Data from the abstracts of hospital records and follow-up visits is always immediately accessible to any member of the staff. Special studies from groups of cases of their choosing are done by house officers and discussed at staff meeting frequently during the course of the year.

#### SUMMARY AND CONCLUSIONS

1. Clinical material in the records of hospital cases must be made easily available if it is to be utilized.

2. A systematic and sustained effort to follow end results in old patients is necessary if need for change is to be recognized and progress in surgery is to be made.

3. A method of surgical follow-up and record keeping is presented which:

a. Gives a satisfactory follow-up in 92.5 per cent of large operative cases over a nine-year period.

b. Makes information from the hospital record and follow-up visits of every group of operative cases easily and immediately accessible.

c. Enables members of the department of surgery to keep in constant touch with immediate and late results in all operative cases.

d. Enables the department to recognize and to alter promptly surgical practices or procedures whose results are not satisfactory.

## SUCCESSFUL LIGATION OF A PATENT DUCTUS ARTERIOSUS

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(From the Department of Surgery and the Department of Medicine, Louisiana State University School of Medicine, and the Charity Hospital of Louisiana)

A REVIEW of the literature prior to 1939 on persistent patent ductus arteriosus shows that a thorough study of the anomaly has been made with regard to frequency, probable origin, clinical symptoms and signs, course, and complications, but that there is an almost complete lack of suggestions for treatment.

Munro<sup>1</sup> (1907) and, later, Graybiel, Strieder, and Boyer<sup>2</sup> (1938) recognized the possibility of surgical correction of this condition. The latter group should be given credit for their attempt at ligation although it was unsuccessful; it should also be noted that their patient had a complicating bacterial endarteritis. In 1938 Gross and Hubbard<sup>3, 4</sup> devised and executed a transpleural operation, which, so far, seems adequate in uncomplicated cases. These authors have reported four ligations without a death. Recently (1940) Jones, Dolley, and Bullock<sup>5</sup> have contributed an interesting report of seven ligations, all successfully accomplished by the technique described by Gross. Although one of these patients died later, the death could not be attributed to the surgical procedure.

We report here another successful ligation of a patent ductus arteriosus by the transpleural technique of Gross, feeling that all such operations should be recorded so that the proper evaluation may be placed upon the results of this procedure.

CASE REPORT.—Miss C. B., a white female, aged 20 years, was admitted to the Charity Hospital on July 20, 1939, for correction of a disabling contracture of the left foot. The corrective operation was performed on Aug. 4, 1939, and recovery was uneventful.

During the routine examination of the patient, the intern, Dr. I. Redler, detected the physical signs of a patent ductus arteriosus and correctly diagnosed the presence of this anomaly, which had also been recognized by Dr. Richard Ashman in 1933 when he examined the patient at the Heart Station of the Charity Hospital.

The patient gave a history of heart trouble since infancy. As a baby she had convulsions which were associated with cyanosis of the lips and face. She had matured slowly and was moderately deaf. She experienced dyspnea and palpitation on slight exertion, but these symptoms had not prevented her from carrying on the usual activities of childhood.

On physical examination the patient was noted to be small in stature and subnormal in development. Physically and mentally she seemed like a 12-year-old child. She presented the physical signs of a widely patent ductus arteriosus without com-

plicating lesions: collapsing pulse of large volume; blood pressure, 130/65; throbbing carotids; and continuous thrill and murmur with systolic accentuation. Both thrill and murmur were widely distributed but were most intense in the second left intercostal space near the border of the sternum. The apex beat was diffuse and forcible but was displaced only slightly to the left. There was neither cyanosis nor clubbing of the fingers.

X-ray films of the chest revealed moderate enlargement of the heart, marked prominence of the pulmonary conus, and a small aortic knob.

An electrocardiogram (Fig. 1), unchanged from one taken in 1933, showed a deep notch on the downstroke of R-1, a definite Q-wave in Leads II and III, and prolongation of the RST interval. The electrocardiogram was not considered definitely abnormal. It was suggested that the unusual form of the QRS might be due to some associated anomaly, such as a defect of the interventricular septum. The blood count and urinalysis were normal.

Operation was decided upon for the following reasons: (1) Obviously the ductus arteriosus was widely patent. (2) It was fairly certain that no other serious anomalies, for which the patency of the ductus might be compensatory, were present. (3) Cardiac enlargement, indicating overwork of the heart and possible future cardiac failure, was present. (4) The patient seemed to be a good surgical risk.

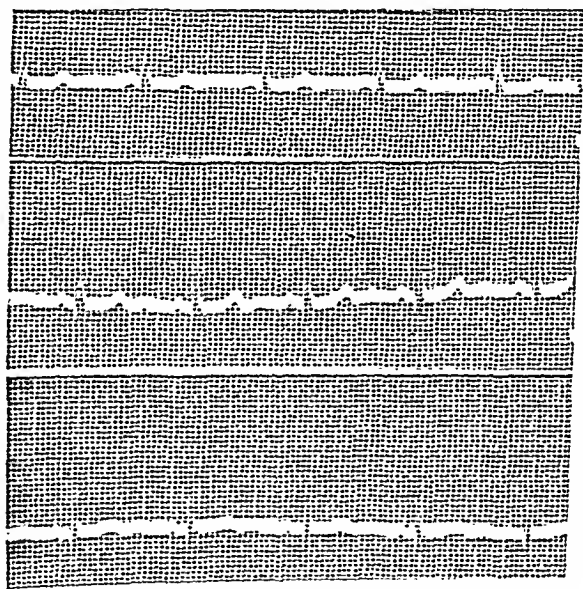


Fig. 1.—Electrocardiogram taken one week before operation (patient C. B. sitting).

Artificial pneumothorax was induced to prevent the consequences of sudden collapse of the left lung at operation. On Sept. 26, 27, 28, and 30 from 300 to 400 c.c. of air were given and the highest reading obtained was + 1.5 on expiration.

Operation was performed on Oct. 2, 1939, under cyclopropane anesthesia. An incision was made in the third interspace, the third costal cartilage was divided, and the third rib was displaced upward. After opening and reflecting the mediastinal pleura, the pulmonary artery was found to be dilated and the walls appeared to be thickened. A distinct continuous thrill was palpable as the pulmonary artery was dissected away from the aortic arch. The ductus was located by applying digital pressure at various levels between the arch and the pulmonary artery until

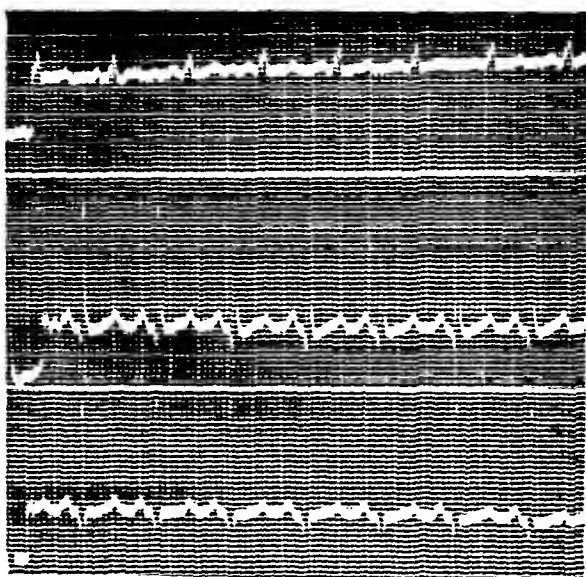


Fig. 2.—Electrocardiogram made immediately after operation. Shift of electrical axis to right, probably due to change in position of heart (patient C. B. recumbent).

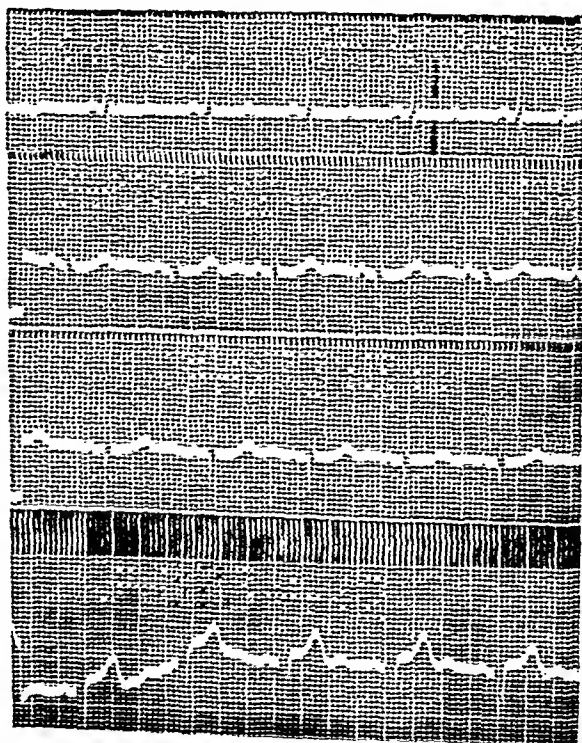


Fig. 3.—Electrocardiogram taken two weeks after operation. T-wave slightly lower than in preoperative tracing (patient C. B. sitting).

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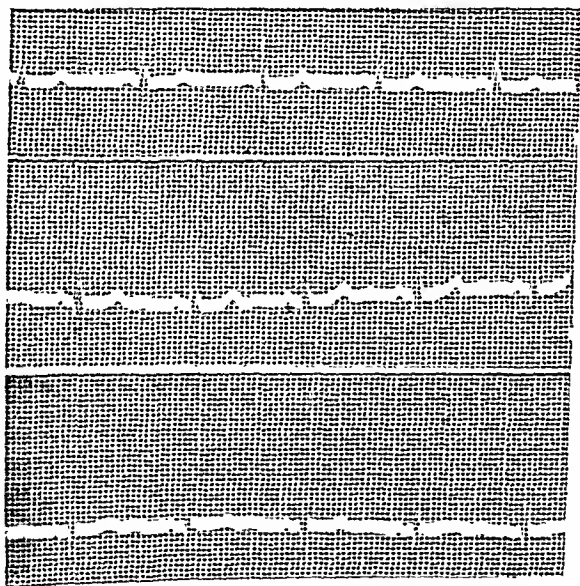


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During convalescence the blood pressure remained fairly constant, from 120/80 to 126/86, the systolic pressure being lower and the diastolic pressure higher than the preoperative levels. The pulse had lost its Corrigan-like character. The thrill and continuous murmur were no longer present but were replaced by a systolic murmur of moderate intensity heard only in the second left interspace.

The sutures were removed on the eighth postoperative day and the patient was allowed to get out of bed.

An x-ray picture taken Oct. 15, thirteen days after operation, showed no change in the cardiac silhouette, the left lung being almost completely re-expanded at that time.

An electrocardiogram made Oct. 17 (Fig. 3) was essentially the same as the tracing made preoperatively.

The patient was discharged from the hospital on Oct. 20, 1939. Since then she has been examined several times, the last time having been on Nov. 14, 1940 (Fig. 4).

On each occasion the physical findings have been essentially the same as those present when she left the hospital. The x-ray picture is unchanged. There is a persistent systolic murmur, which we attribute to dilatation of the pulmonary artery. The patient has returned to her part-time position in an NYA sewing project and reports that, so far as she can tell, she is no better and no worse than before the operation. She feels well but is still made dyspneic by moderate exertion.

#### SUMMARY

The successful ligation, according to the technique described by Gross and Hubbard, of a patent ductus arteriosus in a 20-year-old white female is reported.

Seven months after the operation the patient's status is approximately the same except that there is no evidence of patency of the ductus. The patient may be spared the later development of heart failure, vegetative endarteritis, or other complications of this anomaly.

*Supplementary Note.*—Since the foregoing report was submitted for publication, the authors have had occasion to treat a second patient; unfortunately, fatal hemorrhage occurred in this instance. We report the case briefly because of the technical difficulty encountered after the major part of the operation had been completed.

N. M., a colored male, aged 12 years, was admitted to Charity Hospital on Feb. 27, 1940, with unmistakable clinical, x-ray, and electrocardiographic signs of persistent patent ductus arteriosus.

Operation was performed on July 19, 1940. A ductus about 1 cm. in diameter and approximately 1 cm. long was easily located. Obliteration of the ductus by digital pressure caused the diastolic pressure to rise from 50 to 84 mm., and also caused an immediate cessation of the thrill. All important anatomical structures were carefully identified and isolated with no particular difficulty. The left wall and the anterior and posterior walls of the ductus were cleared quickly, but in separating the right wall from the bronchus, dense connective tissue was found. The ductus was grasped with plain forceps and gentle traction was exerted, care being maintained not to injure the pulmonary artery. A right-angled cystic duct clamp was being used to separate the wall of the ductus from the bronchus when a stream of arterial blood was noticed. In the belief that the ductus itself had been injured, clamps were placed at the aortic and pulmonic ends. There was a gush of arterial blood which could not be checked except by clamping the aorta itself. Death quickly followed.

the thrill disappeared. At the same instant the murmur also disappeared and the diastolic pressure rose from 60 to 80 mm. On releasing the digital pressure, all abnormal signs returned. The ductus was then carefully dissected and was found to be about 12 mm. in length and 8 mm. in diameter. It was ligated at both ends with No. 8 braided silk. The pleura was closed with interrupted silk sutures and the chest wall was closed in layers with interrupted chromic No. 2 sutures. Linen was used for the skin. The left arm was strapped to the chest.

An electrocardiographic tracing made immediately after operation (Fig. 2) showed R-1 and T-1 lower than in the previous electrocardiogram, probably due to the difference in position of the heart. Depression of RST segments in Leads II and III was attributed to the presence of an auricular T-wave.



Fig. 4.—Patient C. B. seven months after operation.

The patient was returned to her bed in excellent condition. Carbon dioxide inhalations were administered every three hours, first as a routine measure, and later because they seemed to benefit the patient.

On the afternoon of the first postoperative day a pericardial friction rub was audible along the left border of the sternum but had disappeared by the afternoon of the next day. This rub was probably due to a small amount of bleeding into the mediastinum.

There was an elevation in temperature to  $102^{\circ}$  on the second postoperative day and a daily afternoon rise for six days thereafter ranging between  $99$  and  $100^{\circ}$ . No special postoperative care was indicated.

During convalescence the blood pressure remained fairly constant, from 120/80 to 126/86, the systolic pressure being lower and the diastolic pressure higher than the preoperative levels. The pulse had lost its Corrigan-like character. The thrill and continuous murmur were no longer present but were replaced by a systolic murmur of moderate intensity heard only in the second left interspace.

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Inspection of the aorta and the ductus showed a friable area of aortic wall adjacent to the right wall of the ductus arteriosus. In dissecting the ductus away from the bronchus, the inflamed area had been torn and attempts to stem the flow of blood with clamps had only increased the size of the tear.

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# Editorial

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## Skin Grafting and the Three-Quarter Thickness Skin Graft

**A**LTHOUGH skin grafting is one of the older surgical procedures, it is remarkable that the surgical profession generally has little knowledge of the good results which can be obtained in the alleviation of many soft tissue deformities by resurfacing the defect with a proper type of skin graft. The various specialty surgeons are more remiss in this respect than the general surgeon. Even many of the plastic surgeons (probably because of the publicity given the pedicled flap) are not always cognizant of the advantages of the usage of a properly selected skin graft.

A more or less simple surgical principle, preparation of a granulating surface for the reception of a skin graft, is often neglected. The fact is lost sight of that a granulating surface has to be surgically clean if a "take" of the skin graft is to be expected and that for cleansing purposes in such instances nothing is superior to a wet antiseptic dressing changed repeatedly or immersion in an antiseptic solution followed by a moist antiseptic dressing.

If one has ever completely excised a heavy scar and noted how much larger the resultant wound is than the central scar, it is easy to understand how a scar tends to contract like rubber and thereby limits movement unless prevented from doing so by underlying anatomical structures. Still much too often this simple principle is not appreciated and therefore the remedy is overlooked; namely, completely replacing the epithelium that has been lost and thereby alleviating the dysfunction. When dealing with healed soft tissue lesions, often there are two reasons for hesitation; either the operator is not dexterous enough to remove a proper graft or he fears the failure of a take.

A new epoch in skin grafting was heralded in 1929 when Blair and Brown introduced their more or less superficial intermediate skin graft, the so-called split graft. Their idea was that one might gain some of the advantages of the full thickness skin graft so far as the properties of good appearance, relative lack of contracture, and fair protection were concerned and that the factor of uncertainty of a perfect take might be eliminated largely as it is with the so-called Thiersch graft. In other words, by cutting a graft considerably thinner than the old full thickness graft and somewhat thicker than the type of skin grafts formerly used, the good properties of each might be combined in this new type of graft and most of the disadvantageous properties might be largely eliminated.

The ideal skin graft should be of such thinness as to assure successful transplantation and leave the donor site capable of spontaneous regeneration and yet be of such thickness as to afford adequate protection and minimum contraction and to match relatively satisfactorily the surrounding skin so far as texture and color are concerned.

However, anyone who has attempted to take an ideal piece of skin with a large knife will admit that often he does not succeed. Besides the inherent human factor and impossibility of controlling absolutely the level of a hand-held knife, much depends upon such factors as the location of the area from which the graft is being removed, the nutrition of the patient, the sex of the patient, the age and even the race. After measuring the thickness of cross sections of a large series of skin grafts taken from the adult male cut with the large skin knife and striking an average, one must conclude that as a rule grafts cut by the hand method, even when trying for depth, vary from 0.008 to 0.016 inch in thickness. Full thickness skin grafts cut by the scalpel in an adult vary from 0.032 to 0.040 inch in thickness.

From microscopic studies it appears that ideally in an adult at least one should be able to sever the skin at a level of from 0.020 to 0.024 inch to get sufficient thickness to approach the qualities of the full thickness graft and still retain the two outstanding good qualities of the superficial intermediate skin; namely, comparative certainty of "take" and the retention of sufficient epithelial elements in the donor bed for re-epithelization. The ideal graft, therefore, to apply on a clean raw surface is a three-quarter thickness skin graft cut at a level from 75 to 90 per cent of the thickness of the skin.

Recently a dermatome has been constructed which, with the utmost facility and ease, allows one to remove a sheet of skin as large as the drum of the dermatoma (4 by 8 inches) and to cut it absolutely of uniform thickness. The thickness can be varied and set at a predetermined level by a calibrating mechanism.

The main advantage of the three-quarter thickness skin graft cut with the dermatome (thickness of 0.020 to 0.024 inch) over the full thickness skin graft on clinical trial has proved to be that a take is a practical certainty if the other factors are observed, such as proper fixation, tension, hemostasis, pressure, and a clean field. Most of the inadequacy of take in the 20 per cent or more of attempts at full thickness skin grafting in difficult areas seems to have been eliminated.

The factor of increased certainty of take has allowed the surgeon to extend the indications for thick skin grafting. It has allowed him to graft successfully such areas as the dorsal and ventral surfaces of the hand and about and between the fingers. Especially in the correction of marked cicatricial deformity about the larger joints, such as the axilla, and also in the correction of other contractures and blemishes,

he can gain greater correction by the use of a three-quarter thickness skin graft of uniform thickness because of the certainty of a take. The fact that one encounters few blistered areas or areas of necrosis so that the subsequent texture and the color are as good as when one gets a partial take improves the functional and cosmetic results, especially on the face and neck. Finally, the fact that the donor area heals within ten to fourteen days from the base is of considerable advantage.

In several situations the thinner type of calibrated graft as removed by the dermatome (0.010 [0.25 mm.] to 0.014 inch [0.36 mm.] in thickness) has distinct advantages over the thinner types of grafts used in the past. Foremost, it allows one to graft successfully the individual with extremely wide denuded areas, a type of case which in the past has often presented a nearly hopeless problem to the surgeon because of his inability to obtain sufficient skin to cover the denuded areas; for example, the type of case with a tremendously large denuded surface covering both thighs and legs with most of the remaining skin on the trunk. The use of the dermatome allows one to remove skin from the abdomen, the chest, the back, or buttocks. It seems that one may use a slightly thicker type of graft (0.014 [0.36 mm.] to 0.016 inch [0.45 mm.] in thickness for example) on a granulating surface so that ultimately the amount of contracture is less and the cosmetic appearance is better. Thus, for the routine case in which it has been customary to use successfully the types of grafts as cut with the large knife, the case, the accuracy, and the quickness of the method recommend the dermatome-cut graft as preferable. In grafting a large cavity it is particularly advantageous to have a large sheet of skin of uniform thickness to drape over the stent. On a small baby one cannot cut by hand with a skin graft knife a graft of sufficient size to be very useful if a large defect is to be covered. With the dermatome a graft of large size may be taken from either the abdomen or the chest. The same may be said in the case of a graft cut from an emaciated person, such as may occur when one sees a severe burn after several months.

Further, if one can vary the thickness of the graft at will, depending upon the region to which it is to be applied and the lesion which one aims to correct, it should prove desirable for varying lesions in different locations to cut a graft of a thickness or a thinness as indicated. And again, according to the age of the patient and the particular region from which the skin is to be removed, a variation in thickness should be desirable as it is well known that the skin of children is thinner than that of adults and that the skin in certain regions, such as the inner thigh of a woman, is thinner. As previously mentioned, for certain lesions it is evident that, if one could remove the skin from any area of the body, such as the chest, the back, or over the ribs, certain areas could be resurfaced in a way not possible by the use of methods commonly practiced.

Finally, and probably most important, due to the invention of the dermatome a new skin graft has become available, a three-quarter thickness skin graft, cut at a level of from 75 to 90 per cent of the thickness of the skin. This graft has advantages over the so-called full thickness skin graft and the superficial intermediate skin graft, especially for giving adequate coverage of aseptic denuded surfaces. The ease with which a skin graft of any thickness may be removed even from areas not previously available simplifies the whole art of skin grafting.

—*Earl C. Padgett, M.D.*

Kansas City, Mo.

# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## RECENT ADVANCES IN THE STUDY AND MANAGEMENT OF TRAUMATIC SHOCK

HENRY N. HARKINS, M.D., PH.D., DETROIT, MICH.

(From the John Simon Guggenheim Memorial Foundation and the Department of Surgery, Division of General Surgery, Henry Ford Hospital)

(Continued from the March issue.)

f. *Plasma (or Serum).*—The transfusion of plasma or serum is not new, being used experimentally by Bowditch (1871) and Luciani (1872). The value of plasma in restoring blood volume after hemorrhage was known to Rous and Turner as long ago as 1918. Plasma has been advised since then by many, including Heinatz and Sokolow (1935); Filatov and Kartaševskij (1935), of the Leningrad Blood Transfusion Institute; an annotation in the *Lancet* (1939); Knott and Koerner (1939); Elliott, Tatum, and Nessel (1940); Elman (1940); Fine and Gendel (1940), in experimental intestinal obstruction; De Gowin, Hardin, and Plass (1940); and others listed elsewhere in this paper. The importance of plasma loss in shock has already been discussed. Its importance in other conditions is also to be reckoned with. The effect of hypoproteinemia in wound disruption has been worked out by Thompson, Ravdin, Rhoads, and Frank (1938).

The observations of Brennan (1940) offer new evidence for the benefit of plasma transfusions. This writer found that: (1) As a result of hemorrhage the individual red blood corpuscles increase very appreciably in size, often by 30 to 50 per cent or more. (2) Following hemorrhage very considerable numbers of the patient's red blood corpuscles become sidetracked within the body, probably in the muscle capillaries. Often more than 20 per cent of the number of those originally circulating were found to be "missing" in this way. Brennan considers that this is because of the inflow into the blood stream of tissue juices of low osmotic pressure which later enter the corpuscles, causing them to swell and clog the capillaries. If these corpuscles could be restored to the circulation, they would correspond to the number that would have been given by the transfusion of a liter of whole blood. Brennan then shows in sixteen cases, mainly neurosurgical patients with extensive blood loss, that plasma transfusions will accomplish this return of lost red cells, and these are in reality a type of autotransfusion.

Finally, and probably most important, due to the invention of the dermatome a new skin graft has become available, a three-quarter thickness skin graft, cut at a level of from 75 to 90 per cent of the thickness of the skin. This graft has advantages over the so-called full thickness skin graft and the superficial intermediate skin graft, especially for giving adequate coverage of aseptic denuded surfaces. The ease with which a skin graft of any thickness may be removed even from areas not previously available simplifies the whole art of skin grafting.

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Neuwelt, Levinson, Olson, and Neeheles (1940) found that successive hemorrhages in dogs and only partial restoration with serum or blood do not permit survival of all animals, while reinfusion with amounts of serum or blood equal to the total volume of blood lost preserved the life of the animal in each instance. Their experiments furthermore showed that serum and blood are of nearly equal value and that in shock from massive hemorrhage maximal rather than minimal amounts of serum or blood should be administered.

The new method of calculating the blood volume of a wounded patient by means of comparing the hematocrit before and after a plasma transfusion, as introduced by Bushby, Kekwick, and Whitby (1940), may have some practical value. A normal-sized man is found on the battlefield and the amount of blood lost is unknown. A plasma transfusion is given; he improves. The question is: Has the plasma transfusion been adequate? How much blood had he really lost? The formula is:

$$V_o = \frac{P \times H_2}{H_1 - H_2}, \text{ where}$$

$V_o$  = Original blood volume just before plasma transfusion, the factor sought

$P$  = volume of plasma given

$H_1$  = hematocrit just before plasma administration

$H_2$  = hematocrit just after plasma administration

EXAMPLE.—A man weighing 70 kg. and whose normal blood volume should be roughly 5,000 c.c. is brought in wounded. The hematocrit readings just before and just after transfusion of 1,000 c.c. of plasma are 44 and 32, respectively. Applying the above formula, the original blood volume on admission is

$$V_o = \frac{100 \times 32}{44 - 32} = 2,666 \text{ c.c.}$$

which indicates that, even with the added 1,000 c.c., the blood volume is still 1,300+ below normal. This formula is open to the objection, however, that a difference of a few points in the hematocrit reading gives great differences in the blood volume. (Thus, with  $H_2 = 34$ ,  $V_o = 3,400$ ,  $H_2 = 36$ ,  $V_o = 4,500$ , and  $H_2 = 38$ ,  $V_o = 6,333$ !) This objection to the formula was not pointed out by Bushby and associates.

*Serum Versus Plasma:* This subject was discussed in a recent editorial (1940). Best and Solandt (1940) stated that as a result of their experimental work they were able to state that plasma and serum were therapeutically identical in shock treatment. Scudder (1940) favored the use of plasma over serum, believing it to be less toxic. Brodie (1900) observed experimentally that there was an immediate reaction to intravenous serum injection, the blood pressure falling. He found that in this regard "serum obtained from plasma is inactive." The use of plasma should be carefully differentiated from that of serum. That reactions occur after the use of lyophilized serum has been reported by Aldrich and co-workers (1938), Lehman (1939), and Ravdin and co-

day to four months, only 1 showed contamination. Following this, 286 specimens of blood were drawn off into centrifuge tubes, and then after centrifuging the supernatant plasma, drawn off into another vacoliter flask. Not a single contaminated specimen resulted despite the double transfer. The use of 1:10,000 merthiolate may explain these excellent results. Elliott, Busby, and Tatum (1940) reported 482 plasma infusions with only 3 reactions. Sturgis (1940) found 1:10,000 merthiolate

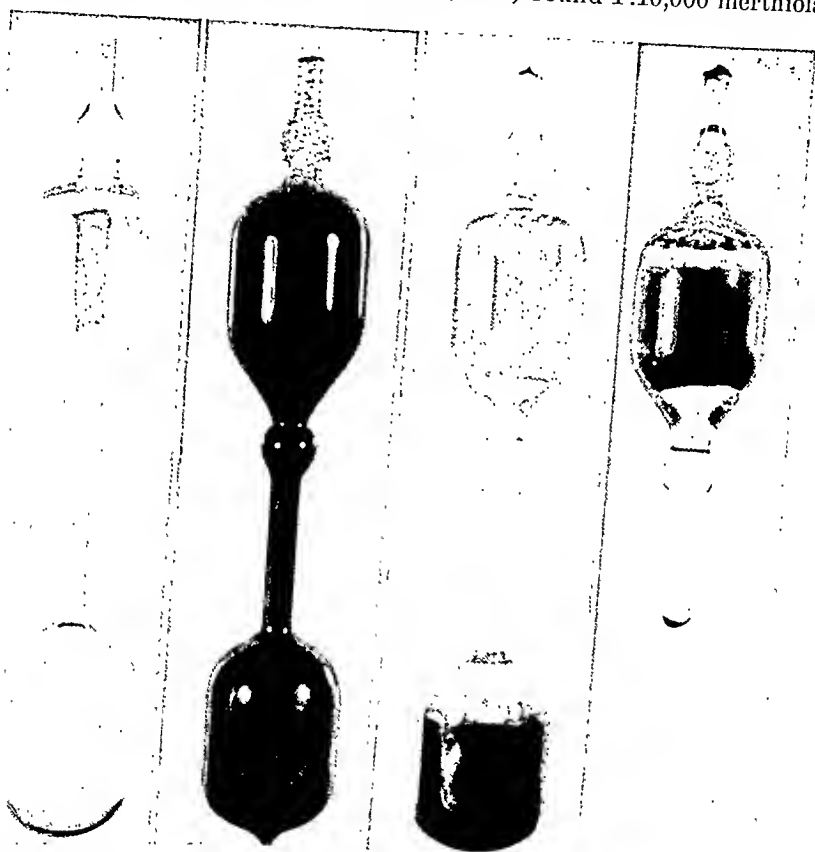


Fig. 11.—The same. Photographs of ampul tubes in process of preparation. (From Crowley, R. T.: *Surg., Gynec. & Obst.* 71: 779, 1940. By courtesy of *Surgery, Gynecology and Obstetrics.*)

to be of little value. One of the newest innovations in the field of serum and plasma therapy of shock is the recent placing of these substances on the market. Thus, one commercial firm offers either human plasma or human serum already prepared in "saftiflasks" in 250 c.c. amounts at \$34.80 per flask.

Bushby, Buttle, and Whitby (1940) found that filtration of plasma through crude asbestos causes clotting due to some unknown factor that can be removed from the asbestos by treatment with 2 N nitric acid. Pure crystalline asbestos (Gooch fiber) does not cause clotting.

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workers (1940). These reactions have generally been attributed to serum changes induced by the lyophile process. Strumia, Wagner, and Monaghan (1940), however, pointed out that serum alone is much more likely to give reactions than plasma. Therefore, they believed that lyophilized plasma is the solution to this difficulty. It would seem that plasma may be preferable to serum. Prejudice against plasma probably arose in the days when citrate preservation was considered dangerous. Now we use it regularly for blood, why not for plasma? The effects of mechanically stirring or otherwise separating serum are much less physiologic.

Several writers prefer serum. Thus, Levinson, Neuwelt, and Neecheles (1940) (experimental article) and Levinson, Rubovits, and Neecheles (1940) (clinical article) favor serum, reporting a low reaction rate. It must be pointed out, however, that their evidence is based on smaller dosages than Strumia's plasma dosages. Clegg and Dible (1940) also favored the use of serum as opposed to plasma. They agree that in the stress of war both are preferable to whole blood, but that certain inherent disadvantages are present in the use of plasma. First, the fibrinogen fraction is unstable and tends to precipitate more and more on standing. In consequence the plasma solution comes to contain particulate matter, making the use of a straining filter essential for its administration. This keeps the plasma mixture from being safely given through a simple tube and funnel in an emergency where more complicated methods, which incorporate a filter in the system, are not available. Second, the separation of plasma from cells involves a good deal of manipulation with a considerable chance of contamination.

Clegg and Dible therefore decided to *convert their plasma into serum*. The serum would combine the advantages of: (1) being able to be given without typing; (2) containing no particulate matter even after long storage at either room or icebox temperature; (3) requiring no filter for administration; (4) being made from bank blood; and (5) passing through a bacterial filter, insuring its sterility.

Advantages 1 and 4 are inherent in plasma as well, and all but the fourth are present in the use of natural serum. Natural serum, however, cannot be made from bank blood. The usual methods of filtering plasma-saline mixtures have proved unsuitable for large-scale and wartime work. As reported by Bushby, Buttle, and Whitby (1940) and others, either the filter becomes clogged or the filtrate, at first clear, later develops a precipitate on standing. Clegg and Dible therefore developed the following technique:

Blood is taken from Group A and Group O donors into a standard bottle of 540 c.c. capacity containing 180 c.c. of 1.05 per cent sodium citrate in 0.85 per cent sodium chloride. The blood is stored in the ice chest for seven to ten days, during which period it is available for transfusion. If not used, the supernatant plasma-citrate-saline mixture is removed by suction in a closed circuit, pooled, and the fibrin pre-

ecipitated by the addition of calcium chloride. Twenty cubic centimeters of 8 per cent sterile calcium chloride per liter of plasma are added with glass beads and the mixture placed in a mechanical shaker. A firm clot separates; the supernatant serum is filtered through a Seitz filter and stored in sterile containers. The resultant serum has the following composition:

Total protein	4.5 to 5.0 Gm./100 c.c.
Calcium	65.0 to 80.0 mg./100 c.c.
Potassium	38.0 to 40.0 mg./100 c.c.

The somewhat high potassium content of this mixture would be theoretically counteracted by the high sodium content. No ill effects have been attributed to the potassium in actual use. Quantities of this serum have been given up to 1,500 c.c. to shock and hemorrhage patients and normal subjects. The only reaction was a transitory urticaria and chill in a normal man given 1,000 c.c. intravenously in fifteen minutes.

Elman (1941) reviewed the use of plasma in severe burn shock. Brennan (1941) pointed out that the plasma requirements of shocked patients cannot always be calculated from a simple blood concentration index such as that of Bushby and associates (1940). Mobilization of sidetracked red cells may cause an actual concentration to follow plasma administration. Tidy (1940), discussing Black's (1940) index of the amount of plasma transfusion in burns on the basis of hematocrit readings, pointed out that the initial hematocrit is an assumption in this index. Hence it is only accurate if the patient's hemoglobin before the burn is normal. The extensive clinical experience with concentrated plasma reported by Hill, Muirhead, Ashworth, and Tigertt (1941) helps to place this mode of shock therapy on a sounder footing. These authors reported a reaction rate of 1 per cent among 299 administrations of concentrated plasma. In 45 cases of shock the results were excellent.

Brown and Mollison (1940), in discussing the current argument regarding the relative merits of plasma and serum, point out that in their experience the dried serum emanating from the Medical Research Council's serum drying unit at Cambridge is not only safe but efficacious. The serum is passed through a Seitz filter before being dried from the frozen state *in vacuo*. In most cases four times normal serum was used. Because it took some time to reconstitute the serum, this process was often done the night before use. In my experience with dried plasma this would be dangerous as the reconstituted plasma tends to gel. Brown and Mollison gave their concentrated serum at room temperature, in doses of 40 to 500 c.c., with 34 reactions following 202 transfusions. In a series of 30 plasma transfusions 8 reactions occurred.

When plasma is given, it may be administered in several forms:

*Natural Plasma:* This was used by Lehman (1939) and others. Strumia, Wagner, and Monaghan (1940) used plasma in over 1,500 administrations without a reaction. In the present vogue for plasma transfusion it is interesting to note, as Robertson (1940) pointed out,

workers (1940). These reactions have generally been attributed to serum changes induced by the lyophile process. Strumia, Wagner, and Monaghan (1940), however, pointed out that serum alone is much more likely to give reactions than plasma. Therefore, they believed that lyophilized plasma is the solution to this difficulty. It would seem that plasma may be preferable to serum. Prejudice against plasma probably arose in the days when citrate preservation was considered dangerous. Now we use it regularly for blood, why not for plasma? The effects of mechanically stirring or otherwise separating serum are much less physiologic.

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a method for drying the serum in the frozen state in cellophane bags. The report of Bond and Wright (1938) on the use of lyophile serum in the treatment of experimental shock and hemorrhage is one of the most convincing bits of evidence in favor of this mode of treatment. Flosdorf and Mudd (1938) have introduced a new type of serum to take the place of the lyophile process; namely, the cryochem serum (from *κρύος* + *χημία*) to designate evacuation *in vacuo* from the frozen state. This new process depends on  $\text{CaSO}_4$  freezing instead of solid carbon dioxide, and reduces the price of a liter of serum from \$3.00 to \$20.00 (by the lyophile process) to 75 cents (by the cryochem process). Amberg and Osterberg (1940) described another method of drying serum; namely, dialyzation against an acacia solution. They must have found it unsatisfactory, because only seven months later Harper, Essex, and Osterberg (1940) reported on another method of preparation of dried plasma used in the Mayo Clinic. This consisted in simple distillation of the plasma at  $45^\circ \text{C}$ . with additional bubbling of sterile air through the plasma. About 400 c.c. could be dried in an hour, and experiments on the final product (using dried dog plasma redissolved) on dogs revealed that it was without reaction when uncontaminated with serum. Dried human plasma, when redissolved, likewise gave no untoward reaction. This method is much simpler and cheaper than the lyophile method.

*Methods of Preparing Dried Plasma (or Serum):* Besides the lyophile and cryochem processes, the methods of Edwards, Kay, and Davie and of Thalhimer, and the two processes used at the Mayo Clinic, numerous methods for manufacture of dried plasma or serum are in use. Preparation of dried serum was begun just at the close of the last war by Burrows and Cohn (1918), who dripped the serum into an evacuated bottle at about the rate that evaporation proceeded. Much the same principle had been used by Martin (1896), of Sydney, Australia, who used a Pasteur-Chamberland filter to drip the serum into the evacuated bottle. He found that under these circumstances the "serum can be desiccated as quickly as it will filter." A method similar to Martin's, only using a funnel with its tip drawn to a fine point, was used by Hartley, Eagleton, and Okell (1923), of the Wellcome Laboratories, London. Shackell (1909) was the first to use the principle of evacuation from the frozen state (sublimation). Greaves and Adair (1936) described a method of desiccation of serum *in vacuo*, the water vapor being removed by  $\text{P}_2\text{O}_5$ . Freezing occurs from evaporation alone, no refrigerants being used. The use of phosphorus pentoxide is not suitable for large volumes of serum, so in 1939 these authors devised a method of high vacuum evaporation in which an electrically measured amount of heat was fed to the frozen serum. This same article gives several other references to this same subject.

The adtevac process of Hill and Pfeiffer (1940), of Dallas, consists in evacuation of serum from the frozen state with additional adsorption of the water vapor with silica gel to hasten the process. Hill (1940) re-

that excellent results were obtained during World War I by the use of cells resuspended in normal saline solution. It is doubtful, however, if these results can be compared with those of more recent times. Weech, Goettsch, and Reeves (1933) used serum transfusions experimentally in dogs for nonshock (nutritional edema, etc.) conditions. Recently Strumia (1940) stated that he believes that plasma transfusions are as useful as whole blood transfusions in all but one emergency clinical condition; that is, carbon monoxide poisoning. Strumia does not type his plasma and has had no reaction in over 1,500 administrations. He restricts its rate of administration to less than 10 c.c. per minute, although he has given 900 c.c. in thirty minutes without reaction.

*Preserved Plasma:* This is merely natural plasma obtained from a blood bank after the blood has been stored. Once separated from the cells, the plasma can be kept almost indefinitely, but it must be filtered before administration.

*Recalcified Plasma:* This is serum made from plasma according to the method of Clegg and Dible. Calcificated plasma might be a more accurate term.

*Dried Plasma, Concentrated Plasma, Reconstituted Plasma:* Dried plasma is a powder. Concentrated plasma is either partially dried plasma or dried plasma reconstituted up to less than its original volume. Reconstituted plasma is dried plasma redissolved in water. Edwards, Kay and Davie (1940), using a method of vacuum distillation without freezing, have recently introduced the use of dried plasma into the British Army. This report indicates the trend toward abandoning whole blood transfusion and substituting the more foolproof and almost, or even just, as effective plasma transfusion. Mudd, Flosdorf, Eagle, Stokes, and McGuinness reported the lyophile process in 1936. Preserved plasma was used experimentally by Mahoney (1938). He performed experiments on the treatment of shock due to peritoneal cooling and to trauma to an extremity. Referring to the former, he stated: "Preserved plasma was compared with whole blood, saline and acacia in the treatment of this type of shock. The plasma was found to be the most efficient therapeutic agent in restoring the normal blood pressure." He found the plasma less efficient in treating shock due to trauma to an extremity.

That serum preserved by the lyophile process can be safely used in large amounts in human beings is attested by the beneficial effects of its administration in a series of lipoid nephrosis patients treated by Aldrich, Stokes, Killingsworth, and McGuinness (1938). In these patients a marked diuresis followed the injection of four times concentrated serum. In a second paper Aldrich and Boyle (1940) confirmed these results. Freeman and Wallace (1938) studied experimentally the effect of concentrated serum on the plasma volume and serum protein concentration. Thalheimer (1939) described a method for concentrating serum in cellophane bags and in a later paper described

present Mayo Clinic method). A summary of the methods of evaporation and sublimation is given by Mason (1940).

The first five methods of pervaporation listed in the table are all variants of Kober's original bag-before-a-fan method. Kober (1917) noted that "collodion and parchment membrane containers permit water to evaporate through the walls as though no membrane were present," and called this phenomenon "pervaporation." It could be hastened by fanning or by heat. This method works fine for *concentrating* plasma, but the last stages of *drying* are interminably long. Terry (1939), for example, merely concentrated and did not even try to dry. Hartman and Hartman (1940) combined the principle of *pervaporation* with that

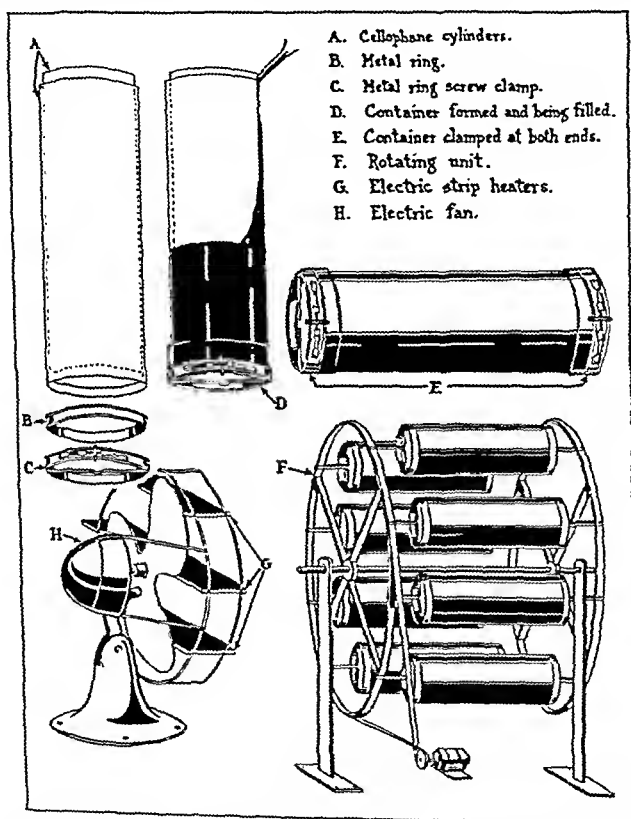


Fig. 12.—The Hartman rotor pervaporator apparatus for desiccating blood plasma. (From Hartman, F. W., and Hartman, F. W., Jr.: J. A. M. A. 115: 1990, 1940.)

of *stirring* in their "rotor plasma pervaporator," shown in Fig. 12. Constant rotation causes frothing with application of a constantly new fluid surface to the exposed cellophane walls. The frothing enables the plasma to be gently rubbed into an easily redissolved powder between the cellophane surfaces when dry; whereas, unfrozen plasma made in cellophane bags or tubes without rotation is apt to cake, and is difficult to put into solution again. This apparatus combines simplicity, econ-

TABLE XIII

## METHODS OF PREPARING DRIED PLASMA OR SERUM: A CLASSIFICATION

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- I. *Spray distillation in vacuo (method of evaporation)*
1. Martin, 1896
  2. Burrows and Cohn, 1918
  3. Hartley, Eagleton and Okell, 1923
  4. Edwards, Kay and Davie, 1940
  5. Aylward, Mainwaring and Wilkinson, 1940
  6. Harper, Essex, and Osterberg, 1940
- II. *Evacuation from the frozen state (method of sublimation)*
1. Shackell, 1909 (prefreezing; chemical desiccant:  $H_2SO_4$ )
  2. Greaves and Adair, 1936 (chemical desiccant:  $P_2O_5$ )
  3. Mudd, Flosdorf, Eagle, Stokes and McGuinness, 1936 (prefreezing; cold condensor desiccant: solid  $CO_2$ ), expensive; suitable only for small quantities; "*lyophile process*"
  4. Flosdorf and Mudd, 1938 (self-freezing; chemical desiccant:  $CaSO_4$ ), "*cryochem process*"
  5. Greaves and Adair, 1939 (no desiccant; electrically controlled application of heat)
  6. Hill and Pfeiffer, 1940 (self-freezing; physical adsorption desiccant: silica gel), "*adterae process*"
  7. Flosdorf, Stokes, and Mudd, 1940 (mechanical desiccation; expensive apparatus; prefreezing optional), useful for large quantities
- III. *Permeation of water through cellophane membrane (method of pervaporation)*
1. Kober, 1917 (bag)
  2. Terry, 1939 (long tube)
  3. Thalhimer, 1939 (long tube), for concentration, warm air; for drying, frozen
  4. Aylward, Mainwaring and Wilkinson, 1940 (long tube)
  5. Best and Solandt, 1940 (long tube)
  6. Hartman and Hartman, 1940 (double surfaced cylinder with rotation), the "*rotor pervaporator*"
- IV. *Miscellaneous methods*
1. Amberg and Osterberg, 1940 (dialysis against acacia)
  2. Hall, Fader and Decherd, 1940 (alcohol-ether precipitation of proteins)
- 

ported that he had given 115 doses of four-times concentrated plasma (9,900 c.e.) prepared by this method with only three transient reactions. Another method of preparing dried serum is that of Hall, Fader, and Decherd (1940), who precipitated the serum proteins with alcohol-ether solution. The serum proteins prepared by this method were injected into dogs and into a single human subject without serious reactions.

Before going on to a general discussion of more methods of drying plasma (or serum), a classification would be in order, as given in Table XIII. It is seen that the methods of evaporation and sublimation are merely modifications of the crudest of all methods, drying in an open dish. Sublimation works well, but excess water vapor is difficult to remove, as testified by the various means to overcome this difficulty. Of the methods of sublimation, the desirae process is best suited for large volume work, the drying capacity of a single unit being 100 liters of plasma a day. Such an apparatus would cost \$18,000.00, while a 10 liter a day apparatus would cost \$3,200.00. Of the methods of evaporation, if the unfrozen plasma is caused to bubble, the result seems better (e.g.,

favored plasma transfusions even for hemorrhage, stating: "In cases of severe hemorrhages the loss of erythrocytes is a relatively secondary factor, one which contributes but little to the state of shock, provided the volume of circulating blood is maintained at a proper level." In their hospital blood is mixed with a 2 per cent solution of sodium citrate in normal saline solution in the proportion of 100 c.c. of citrate-saline mixture to 500 c.c. of blood. Plasma is separated by suction after centrifugation and may be used or stored at 4° C. after addition of merthiolate solution 1:10,000. The plasma is pooled and tested serologically by means of the Wassermann and Kahn tests, but it is not typed or cross-matched. Further discussion of plasma is given under the heading "Shock in Wartime."

3. OXYGEN.—The importance of anoxia was stressed under that heading. At present, administration of oxygen gas from tanks, or better from the liquid state, into a tent or mask is the best method of administration. All shock patients should receive oxygen, possibly with 5 per cent carbon dioxide in cases where respiration is deficient.

4. ADRENAL CORTICAL EXTRACT.—The use of this substance either in the natural or synthetic form has already been discussed. While this method of treatment is still in the experimental stage, it seems to offer great promise. It may act either by reducing hyperpotassemia or by decreasing abnormal capillary permeability.

#### VII. SHOCK IN WARTIME

The tremendously renewed interest in this subject, not only in Europe, but in the United States, is at once apparent from a review of the literature during the past few months. The Medical Research Council (England) *The Treatment of Wound Shock*, M. R. C. War Memorandum No. 1, and the National Research Council (United States) *Bulletin on Shock* are especially important recent contributions. Recent emphasis seems to be on adopting treatment to modern mobile warfare, especially in the use of easily transportable preserved blood or blood factors.

The possibility of use of bovine plasma intravenously in man is discussed by Cohn (1940) and by Wangenstein, Hall, Kremen, and Stevens (1940).

A series of four articles from the Edinburgh and South-East Scotland Emergency Blood Transfusion Service deserves attention. New equipment was described by Stewart (1940) with a reaction rate of 13.6 per cent. Scarborough and Thompson (1940) studied the oxygen capacity of stored blood, concluding: "Neither the haemoglobin content nor the oxygen-capacity of blood is impaired to an important extent by storage under the conditions described for periods up to thirty days." In the final paper Crosbie and Scarborough (1940) found that ten days' storage caused 74 per cent of the leucocytes in blood to be destroyed.

The recent report of Maycock (1940) on the results of the nine blood transfusion services in the Battles of Flanders and France is of interest.

omy, sterility, and rapidity. The double walling of the cylinders alone increases the drying area 100 per cent. While the cylinders usually are opened when needed, the powder poured out and reconstituted in the usual manner, in an emergency the cylinders can be immersed in tap water and the drying process reversed. With the smallest unit of this apparatus 5,400 c.e. of plasma may be evaporated at one time.

*Use of Concentrated Plasma:* Best and Solandt (1940) have extended the use of concentrated serum as used by Aldrich and associates for medical conditions (nephrosis, etc.) to the treatment of traumatic and histamine shock in experimental animals. They believed that the presence of abnormal amounts of fluid in certain tissues during shock is detrimental apart from the loss of blood volume which is represented. Treatment aimed at returning this fluid to the blood stream has long been attempted with hypertonic aqueous solutions. These solutions, however, are themselves apt to leak out through the vessel walls and reverse their action and do more harm than good. From the theoretical standpoint it would seem that concentrated serum might have the desired osmotic action without the deleterious side effects.

Best and Solandt tested this hypothesis on dogs with shock due to (1) histamine, (2) trauma plus hemorrhage, and (3) trauma, using serum concentrated to three times normal. They found that 20 per cent glucose, 3 per cent salt solution, or three times concentrated serum were all more effective in restoring blood pressure than their respective isotonic equivalents, but that the effect of the first two was much more transient than that of the concentrated serum. Finally, they found that a single intravenous dose of pituitrin just before the administration of an adequate quantity of concentrated blood serum seemed to be the best of the treatments studied.

On the other hand, Magladery, Solandt, and Best (1940) found that in posthemorrhagic shock isotonic serum was just as efficacious as concentrated serum. They found that in the treatment of posthemorrhagic shock in dogs approximately 40 per cent of the blood removed must be restored to secure recovery. Comparable volumes of serum or plasma produced equally satisfactory results. They concluded that in their experiments the volume of the red cells restored to the animal is more important than their oxygen-carrying capacity and that serum and plasma were as effective as whole blood. They advised a rapid rate of administration (50 to 100 c.e. per minute) as soon as possible after the hemorrhage of the serum or plasma.

Concentrated lyophilic serum has been used by Hughes, Mudd, and Strecker (1938) and by Wright, Bond, and Hughes (1938) to reduce increased intracranial pressure.

With the British Army adopting plasma transfusions and with the idea in mind that Strumia has used over 1,500 of them without typing, it would seem that plasma transfusions should become the chief item in all shock treatment. Strumia, Wagner, and Monaghan (1940)

of the more chronic cases fresh blood may have been a little better, but not much. Mild reactions occurred more commonly following the use of stored blood than after fresh blood, but severe rigors were practically identical in the two cases (4.7 and 5.4 per cent, respectively). These authors concluded that stored blood should be heated to 37° C. before use, but this conclusion is based on a comparison of only 56 warmed blood specimens with 39 unheated specimens. Furthermore, all reaction rates were higher than in certain other series.

De Gowin, Hardin, and Plass (1940), discussing the storage and transportation of blood for military purposes, stated that blood shipped by transport plane from Iowa City to Oakland, Calif., and return (3,539 miles) was essentially unhemolyzed and reaction-free. Similarly, blood sent by hospital ambulances 500 miles was unharmed. It was found practical to pack ten flasks of blood and the necessary ice in ten-gallon milk cans surrounded by commercial insulating covers. This obviates the use of special equipment in an emergency.

Seudder (1940) and Sturgis (1940) recently summarized the use of plasma in the United States. The latter stated: "I believe ultimately we will be using desiccated plasma in the treatment of shock, probably not diluted up to normal strength, as this will increase the osmotic pressure in the vascular system." Sturgis states that centrifuging of blood to obtain plasma is apt to generate heat causing hemolysis. This can be overcome by the use of dry ice or by using simple settling, the latter giving an approximately 75 per cent plasma yield. Seudder has found the pH of plasma obtained by settling to be nearer normal than that obtained by centrifuging.

Certain very recent publications on the nature of shock may eventually have a wartime application. The observation of Salmon and Engel (1940) that pantothenic acid prevents certain types of hemorrhagic adrenal necrosis due to deficiency states may lead to further discoveries. The recent review of shock by Grodins and Freeman (1941) is of interest. The use of the intramedullary route (into the bone marrow of the sternum, clavicle, tibia, or femur) by Tocantins and O'Neill (1940) is of great interest. These authors used this method in 13 patients. Citrated blood, plasma, glucose and salt solutions were infused without any immediate or delayed local or constitutional reactions.

Rose and Browne (1941) found from experiments on the rat that there is a marked increase in the histamine content of the gastrointestinal tract and a lesser increase in the histamine content of the liver and lung following adrenalectomy. These results may indicate that histamine may bear a relationship to the production of symptoms of adrenal insufficiency and shock and that the metabolism of histamine is influenced by the cortex of the adrenal gland. Boyd, Stevenson, and Watkinson (1938) showed that removal of one-quarter of blood volume of rabbits by hemorrhage did not produce a leucocytosis. Parkins, Swingle, Taylor, and Hays (1938) found that administration of adrenal

Few details are available about the use of plasma, of which there was comparatively little in Flanders. All the officers of the service stressed the advantage of giving adequate amounts and that failure of a severely wounded and shocked patient to recover after 2 to 3 pints of blood or plasma probably means that further quantities must be administered. The highly mobile type of warfare imposed great difficulties upon organization. The need for having each bottle of fluid accompanied by an apparatus for administration was essential under active service conditions.

The number of transfusions given can only be approximated, but it can be said that some 350 to 500 pints of stored blood and plasma were used between May 10 and the evacuation of Dunkerque. Certain technical points merit notice. Cannulation was seldom required (13 per cent at one casualty clearing station and 2 per cent at another), although large quantities of blood were given to single patients. Cannulae were of use during aerial bombardment when restlessness and nervousness increased among the wounded. Prolonged storing of blood, even seven weeks in one instance, seemed to make little difference and reactions were few. Likewise, transportation over rough roads, e.g., 100 miles from Arras to Brussels, seemed to exert no ill effect. The following quotation from one of the Service Chiefs is of interest: "Transfusions were given to patients in beds, on stretchers, in clean rooms, in hovels. . . . Asepsis did not exist, antisepsis in most cases was almost impossible to achieve. I am convinced as a result of this experience that a transfusion could be given in absolutely any circumstances except in a vehicle." And Mayoock doubts the importance of this last restriction. Mayoock finally concludes that either the wounded must be brought to the transfusion centers more quickly or the transfusions must be given nearer the battle line. Since blood requires refrigeration, this second objective is difficult to obtain without resorting to plasma. Brown, Dennison, Ross, and Divine (1940) also reported on the use of blood transfusions in the treatment of soldiers wounded in the battle of Flanders.

The method of blood transfusion described by Bashford (1940) is very applicable to rural or wartime conditions where hospital facilities are not obtainable. Yott (1940) described a method of collecting blood by suction and of administration by pressure which requires only one bottle and hence reduces the chances of contamination and would possibly have a wartime application.

Brewer, Maizels, Oliver, and Vaughan (1940) have recently presented a study on the relative merits of fresh and stored blood. This work comes from the four London Blood Supply Depots (N.E., S.E., S.W., and N.W.). All blood used was obtained from the four depots. Two parts of blood were added to one part of diluent, consisting of 3 per cent glucose in 0.85 per cent sodium chloride and 1.05 per cent sodium citrate. They defined fresh blood as that stored for less than twenty-four hours and stored blood as that more than twenty-four hours old. For acute conditions they found stored blood as useful as fresh blood. For some

cortical hormone was beneficial in adrenalin shock in adrenalectomized dogs. Best and McHenry (1940) have cast a disparaging note on the wave of enthusiasm over histaminase stating that their observations led them to believe that "there was no physiologic basis on which to rest its clinical use."

Williams (1940), working at the Merseyside War Blood Bank, pointed out that, if blood bank bottles were autoclaved along with included citrate solution, the action of the citrate solution on the glass gave rise to an increased alkalinity. This alkalinity leads to hemolysis, but, if the bottles are autoclaved dry, sterility is difficult to obtain, especially as regards the absence of the organism *B. subtilis*. To get around the difficulty, a small amount of distilled water was included in the bottles at the time of sterilization.

The paper of Hill, McMichael, and Sharpey-Schafer (1940) is of great practical as well as fundamental importance. These authors made observations of hemoglobin concentration, blood volume, and blood pressure before and after infusion with normal saline solution, hypertonic saline solution, serum, or concentrated serum in patients with post-operative and post-traumatic shock. They found that physiologic or hypertonic saline solution given intravenously to normal people is rapidly lost from the circulation, while serum is retained in the circulation for long periods. The rise in blood volume is dependent on the quantity of protein added and is not increased by further dilution of the serum. These authors further found that in shocked patients intravenous saline produces transient benefit only, while serum is quite effective. They found the continued elevation of pulse rate in a shocked patient after restoration of blood volume and blood pressure not to be of dangerous import. They believed a rising hemoglobin in shock to be a bad sign while a falling hemoglobin in the absence of hemorrhage is a good sign. Finally, they believed that the retention of infused serum or saline solution can be gauged by observing the changes in the hemoglobin percentage.

The recent article of Solandt (1941) on the work of a London Emergency Blood Supply Depot (of which he directed the S. W. section) is of interest. The S. W. Depot is one of the four London depots and bleeds about 600 to 700 donors a week. Some whole blood is used for transfusion, some plasma is filtered at the Wellcome Laboratories, and the rest of the blood is used for preparation of serum for drying at Cambridge. A blood "depot" and a blood "bank" are essentially the same. The depot system obviates the necessity of bleeding at night or on Sundays and this system has a great advantage when night transport for donors is made very difficult and even dangerous by the blackout and the barrage. Solandt states that it seems likely that "serum will largely replace plasma" in shock treatment. Stetten (1941) discussed the activities of New York City hospitals in sending plasma to Great Britain.

The British M. R. C. Memorandum summarizes its opinion of shock treatment by stating: "It is now generally accepted that the most important requirement for arresting the progressive deterioration in general condition which is such a feature of shock, is restoration of blood-volume and thereby of tissue metabolism." While I might tend to be prejudiced in favor of this statement, I must point out that the question of shock is not yet settled, and, while transfusion therapy is helpful, it is not the entire solution of the problem.

#### VIII. COMMENT AND CONCLUSIONS

A brief definition of shock is the following: A progressive vasoconstrictive oligemic anoxia.

A more descriptive definition of shock is: An oligemia *initiated* by traumatic local fluid loss, either whole blood, plasma, or both; *accompanied* by decreased cardiac output, diminished volume flow, lowered venous pressure, decreased oxygen consumption, arteriolar vasoconstriction, progressive hemoconcentration, capillary congestion, acapnia, and secondary blood pressure fall; and *perpetuated* by a summation of these factors and possibly hyperpotassemia, increased generalized capillary permeability, anoxia, action of tissue metabolites, and deficiency of adrenal cortical hormone. Other changes, both chemical and pathologic, often occur in shock, including increased blood nonprotein nitrogen, decreased coagulability of the blood, and in some instances increase in plasma magnesium.

With all of these changes going on, it is often difficult to tell which are initiating, accompanying, or perpetuating factors. In different clinical conditions the proportionate importance of different causative factors may vary and in some more than one cause may be active. The simplest case seems to be hemorrhagic shock where the loss of fluid is the initiating factor and the other changes act in an accompanying or a perpetuating role. In other cases the loss is chiefly plasma (e.g., burn shock), and in still others it is both whole blood and plasma (e.g., traumatic shock). In some instances the loss of fluid is gradual; in others it is sudden; in some it is greater than in others. In these latter some additional causative factor would seem to be active in producing death; whereas, when the fluid loss is large, it alone may explain the onset of shock and resultant death.

The primary result of the fluid loss is an oligemia with associated vasoconstriction, decreased cardiac output, and decreased blood flow. This latter factor is important in producing an anoxia and resultant general capillary wall and cell injury. A progressive hemoconcentration usually results from the general capillary wall injury and the attendant hyperpotassemia may result from general cell injury. The relations between these and other possible perpetuating factors have been discussed.

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## Book Reviews

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**Cirugia de la Constipacion.** By Dr. Conrado Zuckermann, of the Mexican Academy of Surgery, Professor of Surgical Pathology of the Medical Faculty of Mexico and Surgeon of the Mexican Clinic of Surgery and Radiotherapy. Pp. 189, with 32 illustrations. Mexico, D. F., 1939, Manuel Leon Sanchez.

This monograph represents the work for which the author was awarded the Ricardo Arias medal at the Third Central American Medical Congress in October, 1935. First are presented certain factors thought to be of importance in the etiology of constipation. These include hereditary factors, errors of conduction, errors in alimentation, and local factors, such as parasites and neoplasms. The author stresses the frequency with which constipation is caused by Jackson's veil and various pericolic bands and adhesions. Therapy in milder cases is based on correction of hygienic and dietary faults together with physiotherapy and medications. Cases which fail to respond to these measures fall into the surgical group if accompanied by severe gas pains, toxemia, ptosis, or bands and adhesions. The simplest surgical procedure consists of appendectomy with cololysis or colopexy; a second group requires a short-circuiting procedure; and in a third group hemicolecotomy or complete extirpation of the colon is chosen by the author, who favors spinal anesthesia, wide anastomoses of the open type, and the use of No. 0 or 1 chromic catgut for intestinal suture material.

There follows a chapter dealing with physiology of the large bowel and then a discussion of the various types of sympathectomy for relief of constipation with a description of surgical technique. The next chapter consists of abstracts of pertinent literature beginning with 1923 through 1936. Twenty case histories then are presented with discussion of the surgical procedures employed and the results obtained. In the summary the author claims excellent results in twelve of these cases, satisfactory results in four, and moderate relief in the other four. Many surgeons in this country will criticize the author for his use of heavy chromic catgut in intestinal anastomosis, while others will remain unconvinced that chronic constipation is a surgical disease. The monograph is well written and interesting.

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As one would expect in a book of this type, there is no uniformity of style or method of approach to the subject matter, which gives the book a sense of being disjointed; nevertheless, the articles are well written. The tone of the volume is authoritative. The subject matter is of general interest and will appeal most to the general practitioner. The illustrations are fair. A workable index is appended.

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## Original Communications

### THE EARLY OPERATIVE TREATMENT OF ACUTE HEMATOGENOUS OSTEOMYELITIS\*

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**I**N CONSIDERING the problem of the ideal therapy in acute hematogenous osteomyelitis, one should have a definite idea as to the condition one is proposing to treat and the objectives to be obtained.

In patients over 2 years of age the staphylococcus is the causative organism in about 90 per cent of the cases. This means that until we have evidence to the contrary we must assume that the disease is due to a staphylococcus. This organism is characterized by its ability to necrotize and invade the surrounding tissues. It is also credited with the production of lethal, leucocidal, plasma-coagulating, hemolytic, and fibrinolytic toxins. The human organism has relatively little ability to develop a general immunity to the staphylococcus and there is a definite tendency for this organism to enter the blood stream in large numbers and cause a septicemia which results in the death of the patient in about 70 per cent of the cases in which this complication occurs. In addition to its tendency to cause a septicemia the staphylococcus also tends to enter the blood stream in small numbers and to localize and form metastatic abscesses in various parts of the body. It is further to be noted that living virulent staphylococci may remain dormant in the human tissues for a long period of time and then become active and produce an acute and even fatal infection.

In acute hematogenous osteomyelitis the organisms have reached the bone through the blood stream, either from a focus, usually of little importance, such as a small furuncle or as casual organisms. It is believed

\*EDITOR'S NOTE: This paper and the one by Dr. Wilson which immediately follows it represent two different views on acute hematogenous osteomyelitis. It is interesting to note that, while the two authors differ widely as to the relative importance of the general and the local infection, they approach one another very closely in their method of treating a patient ill with the disease and both warn against precipitous and perhaps harmful surgery on a patient who is exhausted, dehydrated, and toxic.

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which communicates with the general circulation by means of a bony canal appears to be a very efficient mechanism for the introduction of bacteria into the general circulation. Is it not to be expected that a pyogenic infection in bone will be complicated by septicemia more frequently than will a similar infection in the soft tissues?

Not only do pyogenic infections in bone tend to produce a septicemia, but they also tend to cause severe toxemia. This toxemia, which is so characteristic a part of the clinical picture of acute hematogenous osteomyelitis, is caused partly by the toxins produced by the bacteria and partly by the breaking down of the necrotic tissues of the host. The patient remains toxic as long as the local disease is spreading, regardless of whether or not bacteria are entering the blood stream. This toxemia subsides when the local disease is surrounded by a wall of inflammatory tissue which is relatively impervious to the toxic material or when the local disease is adequately drained so that the current is reversed and the toxic material tends to flow out through the wound rather than into the circulation of the host.

An infection on the surface is less dangerous and is accompanied by less toxemia than is a similar infection sealed in the tissues. Consequently, early and adequate drainage of an acutely infected bone is desirable. The question is, can this be done without doing the patient more harm than good? At present the belief is quite widespread that in acute osteomyelitis no operation should be performed until the infection has ceased to spread in the bone and the resistance of the patient has reached a point where an equilibrium is established between it and the infection. Not only is this practice of waiting until the infection has burned itself out supposed to save the life of the patient, but Leveuf,<sup>1</sup> who waits until the temperature is normal before he drains the abscess, claims that this so-called conservative method actually results in less involvement of the bone and that under such treatment sequestration is rare.

It is argued that early operation is inadvisable for the following reasons: (1) The patient is dehydrated; (2) the patient is toxic; (3) the patient is exhausted; (4) it is dangerous to operate upon areas of acute cellulitis; (5) operation tends to increase sequestration; (6) opening the bone forces an overwhelming number of bacteria into the blood stream and tends to cause septicemia or secondary foci; (7) the shock and hemorrhage of the operation lower the patient's resistance; (8) opening the bone does not provide effective drainage; (9) in many patients the disease will subside if it is not operated upon; (10) newer chemical antiseptics, antitoxins, vaccines, bacteriophage, sera, or enzymes will control the infection; and (11) one should wait until the patient develops an immunity to the infection before operating.

that not infrequently a few bacteria break through the natural defenses of the body and enter the blood stream and either pass out through the kidneys or are taken care of by the natural defense mechanisms of the body. Ordinarily, such organisms are never heard from, but in the case of the patient who develops acute osteomyelitis these organisms have settled in the bone and have begun to multiply and kill the surrounding tissues. In the beginning this focus is silent. As the focus increases in size, general symptoms arise from the absorption of the toxic products. These toxic products come from the bacteria and from the necrotic tissues of the host. As the area of inflammation extends outward through the bone to reach the periosteum, local symptoms occur. It is to be noted that the interior of the bone contains no sensory nerves and that pain and tenderness, which are the earliest local symptoms, cannot occur until the inflammation has extended out through the bone to involve the periosteum. It is further to be noted that the appearance of the general symptoms (chill, fever, rapid pulse, toxemia, and general malaise) coincides quite closely with that of the local symptoms.

It is thus evident that, if the focus begins in the bone, the inflammation must extend through the cortex of the bone before it can cause local symptoms and that it must involve a considerable amount of tissue before toxic products are produced in sufficient quantity to cause the severe general reaction which is characteristic of the onset of the disease. From what we know of the growth of bacteria elsewhere, it is probable that the disease is present in the bone for from two to five days, or longer, before any clinical symptoms appear. It is also obvious that either this is an unusually virulent organism or the patient has very slight resistance to this organism, because from the nature of the primary infection the initial dose of bacteria must have been very small; otherwise, general septicemia or a multitude of primary abscesses would have occurred.

The architecture of the bone places the defense mechanisms of the body at a distinct disadvantage in combating an infecting organism such as the staphylococcus. In resisting this organism antibodies appear to play a relatively unimportant role and the burden is borne by the cells, especially the reticuloendothelial cells and the leucocytes. The occurrence of the focus in a rigid nonexpansile compartment prevents the dilation of blood vessels and increase in the local circulation, interferes with the free migration of cells and exudation of serum, and results in extensive thrombosis and ischemia. As a result the body cells die more quickly and the bacteria multiply with greater facility than under similar conditions in soft tissues where expansion is relatively free.

In addition to the above, pressure is generated within the bone. How great this pressure is, I do not know, but the relief obtained by having the canal of a throbbing tooth opened suggests that it is considerable. The presence of positive pressure behind an infected thrombus in a vein

from excessive jarring. The pistonlike effect on the medulla and the jarring can be reduced to a minimum by carefully and gently opening the cortex with a sharp, thin osteotome or with a small drill which is turned at a relatively slow speed and without excessive pressure.

Even under the most favorable conditions there is danger that some bacteria may be forced into the blood stream, but this produces only a temporary bacteremia and I do not believe that there is very much danger that this transient bacteremia will cause secondary foci or a continued septicemia.

While the conditions are not entirely comparable, it is to be noted that Reichel<sup>4</sup> has shown that staphylococci injected into the circulation of the rabbit are nearly all removed by the reticuloendothelial cells within forty minutes after the injection and that the positive blood culture will not persist unless there is a focus of infection which continues to pour bacteria into the blood stream or unless the bacteria actually multiply in the circulating blood. The conditions are not quite comparable because the resistance of the patient to the staphylococcus is much less than is that of the normal rabbits which Reichel used. However, the patient's resistance is not so low that the forcing of a single shower of bacteria into the blood stream will produce a continued septicemia. For this to occur it is necessary for the bacteria to multiply in the circulating blood faster than they can be destroyed by the defense mechanisms of the body, and when this condition is present the patient is doomed, unless we can treat him with some agent which either kills the bacteria in the blood stream or at least prevents them from multiplying.

7. It is true that the shock and hemorrhage incident to the operation will tend to lower the patient's general resistance. However, if the operation is planned beforehand and is performed skillfully, it can be done in a few minutes and relatively little blood need be lost. Also, the amount of blood lost can be replaced immediately by transfusion when this is indicated.

8. It is true that where the infection is disseminated through cancellous bone it is not possible to drain this bone effectively by removing a window in the cortex. However, in such an instance partial or incomplete drainage is better than no drainage at all. It has been my experience that after opening such a focus it is usual that the drainage becomes well established within a few days and the temperature falls slowly and the patient improves gradually rather than by a crisis.

9. In answer to the statement that in many of the patients the disease will subside if not operated upon, I have seen one such patient who had a very low grade infection in the shaft of the tibia which was treated by rest. This patient was treated conservatively against my advice and the clinical signs subsided and a small abscess cavity appeared in the bone

On the above eleven reasons I wish to comment as follows:

1. It is true that many of these patients are dehydrated when they enter the hospital and it is also true that surgery should not be performed on such patients. However, it is possible to correct the dehydration within a few hours by the administration of intravenous salt solution and glucose and this should be done on dehydrated patients before they are operated upon.

2. The patient may also be severely toxic, even after the dehydration has been corrected. It has been shown by Joyner and Smith<sup>2</sup> that a relative increase in the nonsegmented (immature) leucocytes and a relative decrease in the segmented (mature) leucocytes is the best measure of this toxicity and that usually this can be corrected by the administration of large doses of staphylococcus antitoxin. The antitoxin is given when the immature forms constitute 20 per cent or more of the total number of leucocytes and its administration is continued at intervals as long as this abnormal condition persists. However, the toxicity is not a contraindication to operation and severely toxic patients who are not dehydrated and exhausted should be operated upon and the bones should be drained in order to decrease the amount of toxin which is being poured into the general circulation.

3. It is also true that the patient may be exhausted by the constant pain. Consequently, he should be given a full dose of morphine and put at rest and the involved extremity should be immobilized while the dehydration is being corrected. This also requires only a few hours.

4. In a previous paper<sup>3</sup> I have stated that I do not believe that it is dangerous to incise an area of acute cellulitis if the incision is cleanly made with a sharp knife and the part is put at rest and the wound is left open after the operation. The mechanical forces exerted in making such an incision are very different from those exerted in squeezing a boil and I do not believe that the incision is liable to force bacteria into the blood stream and produce a septicemia. As a matter of fact, if the incision is left open the local blood and tissue fluids flow out through the incision and bacteria present in the incised tissues tend to move with this current rather than against it.

5. The statement that drainage of the bone tends to increase the amount of sequestration is so contrary to surgical principles and so at variance with my own observations that I do not believe that it is founded on adequate clinical observation.

6. There is some justification for the belief that opening the bone in an acute osteomyelitis tends to force large numbers of organisms into the blood stream and there is no doubt but that this is the most valid reason for deferring operation. The danger arises from the sudden temporary increase in the intramedullary pressure which occurs when a surgical instrument is violently driven through the cortex into the medulla, and

11. In regard to the statement that one should wait until a patient develops an immunity to the infection, I have emphasized the fact that the defense of the body against staphylococci infection is not of the same order as is the immunity to some other types of bacteria, but is largely a cellular phenomenon involving phagocytosis and the walling off of the infected area. It is also true that many patients never develop an effective immunity to this organism, even though they may harbor it over a period of many years, as is evidenced by the chronicity of the disease and by the fact that in patients with chronic osteomyelitis the disease tends to flare up and that, after having harbored the disease over a period of years, these patients may develop acute infections and even septicemia which may prove fatal. Forssman<sup>7</sup> has stated that the staphylococcal immunity which does develop is a very slow process and takes not less than thirty days in rabbits.

In consideration of the above statements, when a patient is suspected of having acute hematogenous osteomyelitis, this patient is a surgical emergency and he should be seen by a surgeon at the earliest possible moment and taken to the hospital immediately. When he enters the hospital he should be given a full dose of sulfathiazol by mouth or of sodium sulfathiazol intravenously and his general condition should be estimated. If he is exhausted and dehydrated, he should be given ample sedation and ample intravenous fluids. If he is extremely toxic he should be given a large dose of staphylococci antitoxin according to the principles laid down by Baker and Shands<sup>5</sup> and the extremity should be immobilized and the patient put at rest for a few (usually eight to twelve) hours, or until the dehydration and exhaustion can be corrected. He should then be taken to the operating room, handled as gently as possible, and the limb draped and prepared for operation before the anesthetic is started. If the surgeon prefers, the operation can be performed under local anesthesia.

As a rule, no tourniquet is used in acute pyogenic infections, because it is not wise to traumatize the limb by the tourniquet.

The bone in the suspected area should be exposed by the most direct route with as little damage to the surrounding tissues as possible. The incision should be ample, but not excessive in length. Whether or not pus is encountered after incising the periosteum, the medulla of the bone should be opened. In younger patients in which the focus is near the end of the bone I use a sharp thin osteotome, cutting out a window with the corner of the osteotome. In older patients or in locations where the cortex is thick I first make multiple drill holes in the cortex and then connect these by cutting out the intervening bone with the osteotome. A small drill point is used first and this is followed by one about  $\frac{1}{4}$  inch in diameter. Every effort is made to handle the bone as gently as possible and to avoid excessive pounding on the bone or a sudden increase in the intramedullary pressure.

and this disappeared over a period of about six months. This patient was an exception and not the rule, and I would advise operation again under similar conditions. I think that the risk was much greater in leaving this patient without operation than it would have been had he been operated upon promptly. When drainage is not instituted, the patient continues to absorb toxic material from the bacteria and from the degenerating tissues. If the area involved is small and the organism is not very virulent, the resulting toxemia is not important, but, on the other hand, it is not desirable. When a large area is involved by a very virulent organism, the toxemia may be profound and may endanger the life of the patient unless drainage is instituted.

10. Of the newer chemical antiseptics which have been tried, sulfanilamide has a definite bacteriostatic effect upon susceptible streptococci and sulfathiazol is effective against both staphylococci and streptococci in the blood of infected animals. For this reason patients with acute osteomyelitis should be given full doses of sulfathiazol and this should be continued until the fever has subsided. However, it is not to be expected that this drug will reach the focus in the bone in sufficient concentration to be effective, because this focus contains large numbers of bacteria and is separated from the general circulation by a relatively impermeable wall of inflammatory tissue. Consequently, the bone focus should be drained whether or not this drug is used.

In regard to antitoxins, the recent work by Baker and Shands<sup>5</sup> indicates that antitoxin will reduce the mortality of staphylococcal septicemia associated with osteomyelitis. In their series the mortality without antitoxin was 70 per cent and with antitoxin was 25.7 per cent. However, they emphasize the fact that if antitoxin is to be successful the focus should be drained early in order to reduce the amount of toxin which is being poured into the blood stream.

Vaccines cannot be expected to help an acute infection (if for no other reason, because of the time element) and the same is true of toxoid. To give an acutely ill patient vaccine or toxoid is to attempt to stimulate an exhausted defense mechanism by adding to the burden which is already straining it nearly to the breaking point.

Bacteriophage appears to be without clinical effect on these infections in the bone. Sera, which are now in the experimental stage and which have for their purpose the destruction of the staphylococci in the blood stream, may prove to be of great value, but even with the use of such sera early drainage of the focus is advisable in order to decrease the number of organisms and the amount of toxic material entering the blood stream. The recent work on an extract of a soil bacillus, probably an enzyme, by Dubos<sup>6</sup> may eventually prove to have a beneficial effect on osteomyelitis.

11. In regard to the statement that one should wait until a patient develops an immunity to the infection, I have emphasized the fact that the defense of the body against staphylococcic infection is not of the same order as is the immunity to some other types of bacteria, but is largely a cellular phenomenon involving phagocytosis and the walling off of the infected area. It is also true that many patients never develop an effective immunity to this organism, even though they may harbor it over a period of many years, as is evidenced by the chronicity of the disease and by the fact that in patients with chronic osteomyelitis the disease tends to flare up and that, after having harbored the disease over a period of years, these patients may develop acute infections and even septicemia which may prove fatal. Forssman<sup>7</sup> has stated that the staphylococcal immunity which does develop is a very slow process and takes not less than thirty days in rabbits.

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It is to be emphasized that this operation is for drainage only and that no attempt is made to remove the infected and necrotic bone. If there is extensive disease in the medullary cavity and the patient is in good condition, a relatively long window is made in the cortex. After hemostasis has been effected, the wound is sprinkled generously with powdered sulfathiazol and is packed loosely with vaseline gauze and the extremity is immobilized either in a plaster-of-Paris cast or a very voluminous dressing and splint or by traction.

The anesthetic is continued no longer than is necessary. Postoperatively the patient is given intravenous fluids and if the red blood cell count is low he is given repeated small transfusions. Also, the large doses of antitoxin should be continued as long as the nonsegmented leucocytes are relatively increased in the blood (over 20 per cent).

I believe that it is better surgery to operate early in this manner on a patient with suspected osteomyelitis and to open a normal bone occasionally than it is to wait until the disease has progressed to a point where the diagnosis is obvious. I believe that this type of treatment not only will decrease the mortality, if it is carried out with judgment by a skillful surgeon, but it will prevent much chronic osteomyelitis and will lessen the number of joints which are destroyed by the disease, lessen the number of secondary foci, and lessen the amount of destruction in the bone which is primarily infected. It is thus evident that the most effective measures at hand for the prevention of chronic osteomyelitis with its resultant crippling are the early diagnosis and prompt and effective drainage of acute osteomyelitis (Key<sup>8</sup>).

In patients under 2 years of age the patient is treated as described above, but operation is usually delayed until an extraosseus abscess appears and then this is drained and the bone is not disturbed. In some infants with a mild infection incision and drainage may be omitted entirely. This is because in infants the bone contains large canals and relatively little inorganic matter and the infection acts much as does an infection in soft tissue. It quickly forces its way through the bone and the extraosseus abscess is formed relatively early. Since the bone is very porous, that which is killed tends to be absorbed without sequestration. A second reason why sequestra are rare in infants is that about one-half of the cases are caused by streptococci and infection in bone by these organisms tends to heal without the formation of sequestra.

In conclusion I wish to acknowledge our debt to those students of the disease who have advocated the delayed operative or conservative treatment of acute hematogenous osteomyelitis. Their efforts have borne useful fruit in that they have made us osteomyelitis-conscious, have caused us to think logically about the disease, have stimulated us to study the reaction of the animal organism to pyogenic infections, and have forced us to consider our patient as a whole and so to improve our treat-

ment that the patient is not operated upon until the dehydration and exhaustion have been corrected and he is ready for the operation. But he is prepared for the operation as promptly and thoroughly as possible, is operated upon with the least possible trauma, and is so treated afterwards that he is given the best chance, not only to live, but to live as a normal human being.

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## THE DELAYED OPERATIVE TREATMENT OF ACUTE HEMATOGENOUS OSTEOMYELITIS

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A DETAILED study of 110 patients suffering from acute hematogenous osteomyelitis was made in 1935 in an attempt to determine the proper time for drainage. This disease has long been considered a surgical emergency and it was hoped through this investigation to prove or disprove this dictum. It has recently been possible to study 33 patients who were admitted to the orthopedic wards of the Children's Hospital since the 1935 report was prepared. This analysis will be directed chiefly toward this latter group. We have held the conviction that acute hematogenous osteomyelitis was a disease of the organism as a whole and not entirely a pyogenic infection involving one or more bones. The acuteness of the onset of the disease, with a severe constitutional reaction, and as a rule bacteria which may be recovered from the blood stream are proof of a general infection. The fact that the organisms have a predilection for bony structures instead of soft tissues should not be the governing factor in the management of the disease. The infecting bacteria are blood borne from a focus, such as a furuncle, an abrasion which has been neglected and allowed to become sealed over, from urinary infections, and, in fact, from almost any type of pyogenic lesion.

The bacterial emboli lodge in the diaphyses. At this point one of two things may happen. Resolution may occur or an abscess requiring surgical drainage may develop. Once the infected embolus lodges, the usual histologic changes of acute inflammation occur in the tissue. Liquefaction takes place at the point of bacterial invasion. This is followed by round-cell infiltration and later, if the process continues, by true abscess formation. These points must be kept in mind when determining the proper time for drainage.

### CHEMOTHERAPY

The use of sulfanilamide, sulfapyridine, sulfametathiazol, and sulfathiazol must be discussed in the treatment of the acute phase of this disease. Our experience is too limited as yet to draw definite conclusions regarding the efficacy of chemical agents. Patients with clinical signs of acute osteomyelitis have shown progressive x-ray evidence of the disease although the constitutional symptoms seemed to abate more rapidly under the influence of the drugs. The careful use of sulfanilamide in streptococcus infections and sulfathiazol in staphylococcus infections with bacteria in the blood stream is recommended. Administra-

tion should not be instituted until the type of infecting organism has been determined. The alert clinician will familiarize himself with the toxic manifestations of these drugs, taking frequent blood counts and blood concentrations of the chemical. Administration of powerful agents is not without danger but is proper when the infecting organism has been determined.

Roentgenograms of three patients from the Orthopaedic Department of the Los Angeles General Hospital are introduced to emphasize the fact that the local lesion may not be greatly influenced by the use of chemical agents. Fig. 1 shows the changes occurring in the ilium of a girl, 10 years of age, ill for five weeks at the time the first roentgenogram



Fig. 1.—X-ray of ilium, Aug. 30, 1940, of a female, 10 years of age, who became ill Dec. 21, 1939. *Staphylococcus aureus* bacteriemia. Treated with sulfathiazol; 2,400 c.c. of blood in ten transfusions. Afebrile March 1, 1940.

was taken. Fig. 2, taken a little more than two months later, shows a marked increase in bone destruction, although the patient during the interval did not manifest signs or symptoms of an acute febrile affection.

Figs. 3 and 4 are roentgenograms of a lesion of acute hematogenous osteomyelitis of the neck of the femur in a boy 8 years of age. Despite the fact that acute symptoms have subsided, bone disintegration is progressing.

Figs. 5 and 6 are roentgenograms of the femur of a boy, 2½ years of age, who became ill on Sept. 27, 1940. A prompt recession of constitutional symptoms followed the use of chemotherapy. The bone changes show a progression of the disease.

One should not be lulled into a state of false security by the sudden amelioration of the toxic symptoms following drug therapy in acute



Fig. 2.—X-ray of same patient as shown in Fig. 1, taken April 4, 1940.

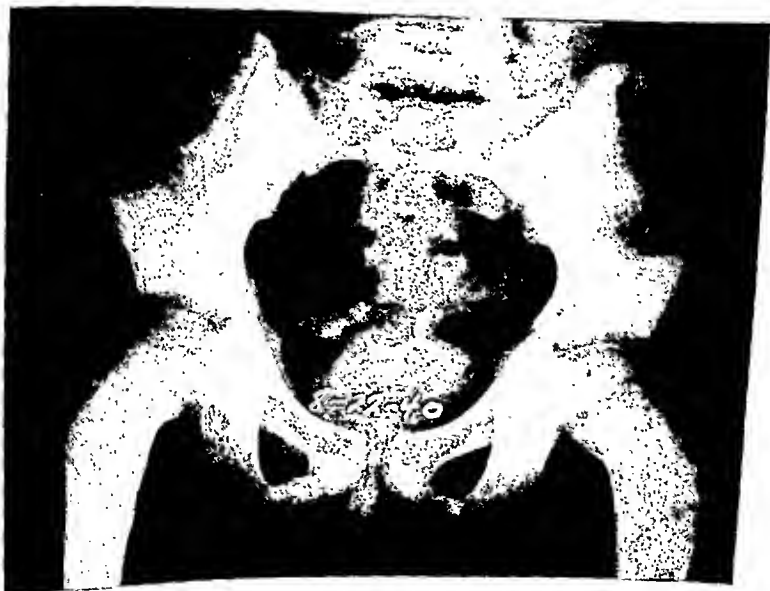


Fig. 3.—X-ray of head and neck of femur taken Aug. 22, 1940, of a boy 8 years of age. Became ill July 9, 1940. *Staphylococcus aureus* recovered from the blood stream. Treated with sulfapyridine. Became afebrile Nov. 1, 1940.



Fig. 4.—Same patient as shown in Fig. 3, seven weeks later. Note progression of bone destruction.



Fig. 5.—X-ray taken Oct. 14, 1940, revealing a lesion of the upper end of the femur of a boy, aged 2½ years, who became ill Sept. 23, 1940. *Staphylococcus aureus* recovered from blood stream. Treated with sulfathiazol. Became afebrile Oct. 13, 1940.

hematogenous osteomyelitis. The necessity for drainage of abscesses at the proper time still exists.

Sulfanilamide and sulfathiazol may be considered valuable agents in that they help to stay the hands of the surgeon for a short time while the patient musters his own protective forces.

The operation which in due course becomes necessary should be thoroughly carried out to obtain drainage. Incision of the periosteum or drainage of the abscess cavity by drill holes is not adequate. It is preferable to preserve the periosteum by elevating it with an instrument and then remove a window of bone with a chisel or gouge. A reconsideration of the pathologic changes must further impress one with the fact that protective barriers, so far as possible, must be saved.



Fig. 6.—Same patient as shown in Fig. 5, x-ray taken Nov. 8, 1940. Continued destruction.

In order to bring out the salient factors under discussion, attention is directed to an analysis of 33 consecutive patients suffering from acute hematogenous osteomyelitis who have been admitted to the orthopaedic wards of the Los Angeles Children's Hospital since 1935. These patients were white and varied in age from 17 months to 12 years. Thirteen were females and 20 males. A definite preosteomyelitic history of furuncles was obtained in 4 cases; of urinary infection in 9; of superficial infections, such as blisters, splinters, and scratches in 5; of impetigo in 2; of otitis media in 1, chicken pox in 1, laryngitis in 1, making a total of 23. The remaining 10 gave no history of any condition which might be construed as a forerunner of acute osteomyelitis.

From Fig. 7 it is seen that 22, or 66.6 per cent, suffered from single diffuse lesions. Eleven, or 33.4 per cent, had more than one diffuse lesion. No case in this series of 33 developed more than one metastatic lesion. This is in marked contrast to the 1935 series, for in this group 6 patients had two lesions, 1 patient three lesions, 2 had four, 1 had five, and 1 had six bone lesions.

The streptococcus was not a frequent cause of the disease. The staphylococcus was the predominating organism. The hemolytic *Staphylococcus aureus* was the infecting organism in 19 patients, the *Staphylococcus aureus* in 8, the hemolytic streptococcus of the beta type in 3, the hemolytic streptococcus alpha type in 1, and mixed alpha and beta types in 1 patient. The hemolytic *Staphylococcus citreus* was recovered in pure culture in 1 case.

Organisms were recovered from the blood stream in 19 patients. The hemolytic *Staphylococcus aureus* was found 13 times, the *Staphylococcus aureus* 4 times, and the hemolytic streptococcus beta type in 2 instances.

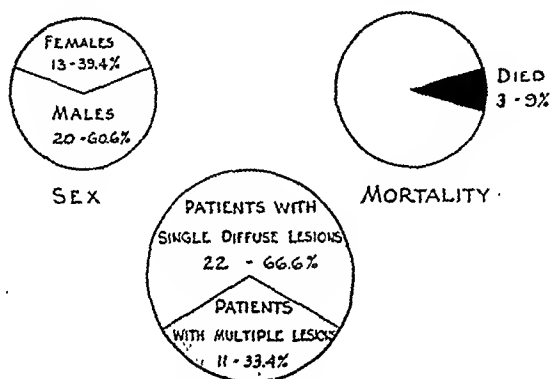


Fig. 7.—Classification of patients.

The bones of the lower extremities were most frequently involved. This was particularly true of the femur and the tibia which were involved, respectively, in 9 and 15 patients. The infection developed in the proximal end of the tibia in 6 patients and in the distal end in 9 patients. The order was reversed in the femur, 7 lesions occurring in the upper end and 2 in the lower. The fibula was involved 4 times, the focus occurring in every instance about the distal metaphysis. The ilium and the os calcis were each involved in 1 instance. The bones of the upper extremities were involved in 3 individuals, the emboli lodging in the clavicle, humerus, and ulna. This gives a total of 30 primary lesions in the lower extremities and 3 in the bones of the upper extremities.

The time of operation seems to have a definite bearing upon the mortality. In order to discuss this the patients have been divided into four groups with respect to the time of surgical drainage after the onset of the disease.

Group I is composed of the patients operated upon during the first seven days of their illness. Eight out of 33, or 24 per cent, come in this classification. Five of these patients, or 62.5 per cent, developed no metastatic lesions. Three out of the 8, or 37.5 per cent, developed one metastatic lesion following operations for drainage of the primary focus. Two, or 25 per cent, died following drainage.

Group II includes 18 patients, or 54 per cent, who had operative drainage between the seventh and fourteenth days of their illness. Eleven of these 18, or 61 per cent, had no metastatic lesions, while 7, or 39.9 per cent, had one metastatic lesion. There were no deaths in Group II.

Group III includes patients whose abscesses were drained between the fourteenth and twenty-first days of their illness. Three patients may be placed in this classification. Two, or 66.6 per cent, had no metastatic lesions. One, or 33.4 per cent, had one metastatic lesion. There were no deaths in this group.

Group IV includes those patients with acute osteomyelitis who, for one reason or another, were not drained. Spontaneous rupture occurred in 3 cases and 1 died twenty-four hours after admission. While the patient had osteomyelitis of the tibia, bronchopneumonia was also well developed and there was no clinical evidence to prove which first appeared. At any rate, this group had a mortality of 25 per cent.

DRAINED FIRST 7 DAYS 8 PATIENTS 24%	GROUP I	
	NO METASTATIC LESIONS 5 - 62.5%	1 METASTATIC LESION 3 - 37.5%
	DIED 2 - 25%	
DRAINED 7" TO 14" DAY 18 PATIENTS 54%	GROUP II	
	NO METASTATIC LESIONS 11 - 61.1%	1 METASTATIC LESION 7 - 39.9%
	DIED NONE	
DRAINED 14" TO 21" DAY 3 PATIENTS 9%	GROUP III	
	NO METASTATIC LESIONS 2 - 66.6%	1 METASTATIC LESION 1 - 33.4%
	DIED NONE	
NO DRAINAGE 4 PATIENTS 12%	GROUP IV	
	NO METASTATIC LESIONS	
	DIED 1 - 25%	

Fig. 8.—Time of drainage.

#### FATAL CASES,

A brief discussion of some of the salient points in the histories of the patients who died is of interest.

Attention is first directed to a female child, 3 years of age, who developed acute hematogenous osteomyelitis of the distal metaphysis of the fibula following impetigo. Hemolytic staphylococci were recovered from the blood stream. Five days after the onset of the disease the fibula was drained and nine days later the child died. Post-mortem examination revealed a bilateral bronchopneumonia and suppurative pericarditis. There was no clinical evidence of pneumonia or pericarditis at the time the drainage was done. One must be impressed by the fact that osteomyelitis of the fibula is not an extensive lesion. Perhaps further supportive treatment would have enabled this patient better to localize the infection, thereby preventing the fatal complications. An

early surgical procedure might easily disseminate infection; whereas, the formation of further protective barriers in a few days could have made it safe.

The second fatal case is that of a Mexican boy, 2½ years of age who developed acute osteomyelitis of the left upper tibial metaphysis on Sept. 11, 1935, following pyelitis. *Staphylococcus aureus* was recovered from the blood stream by culture. The tibia was drained four days after the onset of the disease, and six days after the onset of the disease the patient died. The autopsy revealed bilateral bronchopneumonia, a suppurative pericarditis, and a suppurative arthritis of the left knee joint. While it is admitted that he was from the beginning very acutely ill, it must be conceded that the operation for drainage was untimely in the light of the post-mortem findings. The end results might have been the same in any event, but this case clearly illustrates the fact that the bone abscess was only a small part of a severe general infection. It is conceivable that the shock arising from the surgery did not aid recovery.

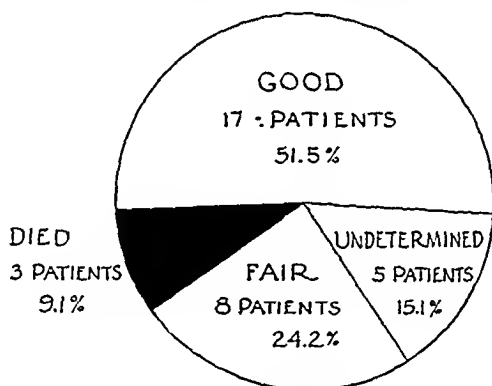


Fig. 9.—Final results.

The third patient was moribund on admission and died the following day from bronchopneumonia. No operation was performed, even though she exhibited a well-defined osteomyelitis of the upper tibial metaphysis. Elimination of this case would reduce the mortality in this series of 33 patients to 6 per cent.

#### END RESULTS

The results of this disease as far as they can be determined at the present time have been classified as good, fair, and fatal. Mortality has been discussed and may be considered to be either 6 or 9 per cent. The good results are those in which the bone infections are now healed. Fair results are those in which drainage from the infected bone still persists and in which the general condition of the patients is reasonably good. There were none who seemed to fall into a category which might be described as poor.

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	DIED NONE		
NO DRAINAGE 4 PATIENTS 12%	NO METASTATIC LESIONS		IV
	DIED 1 - 25%		

FIG. 8.—Time of drainage.

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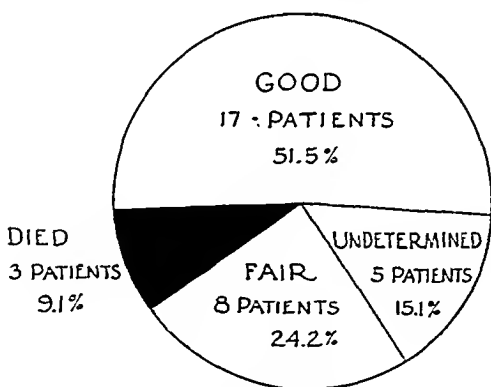


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After eliminating the 3 fatal cases with a mortality rate of 9.1 per cent, those remaining may be graded as follows: Seventeen patients, or 51.5 per cent, fall into the classification of good results at this time, and it must be taken into consideration that a number of these cases are fairly recent. Eight patients, or 24.2 per cent, at this time may be classified as fair results. It is very likely that at least one-half of these will be classified as good results within six months. Five patients, or 15.1 per cent, have disappeared so that no information concerning their present status could be obtained.

### CONCLUSIONS

Acute hematogenous osteomyelitis is a serious disease. Primarily we fear the loss of the patient and subsequently the prolonged illness with draining sinuses and disabling deformities. These may be due to the direct involvement of joints, fibrous changes in soft tissues with contractures, and directional changes due to disturbances of the epiphyses.

The use of sulfanilamide and sulfathiazol is recommended, providing the type of infecting organism is known. The patient's blood must be frequently examined and the clinician should be on the alert for other toxic manifestations of the drug.

The mortality was greatest in Group I in which surgical drainage was performed within seven days after the onset of the illness. In Group II, the largest one, there were no deaths and it is believed that the infections were equally severe. In Group III, although a small one, there were no deaths.

Drainage will be in order when all signs of dehydration have been overcome, when the location of the focus can be determined with some degree of certainty, and when there is reasonable evidence that pus is present.

Come what may, the surgeon should not lose his balance and be stampeded into an inexpedient operation simply because he has a patient with septicemia who develops an abscess within the substance of bone.

## FIBROSARCOMA OF THE SOFT PARTS OF THE EXTREMITIES

STEPHEN A. ZIEMAN, M.A., M.D., CHICAGO, ILL.

(From the Department of Surgery, Rush Medical College, University of Chicago)

IN RECENT years several important papers have appeared in the literature on fibrosarcoma of the soft parts of the extremities.<sup>1</sup> A number have surveyed the subject with thoroughness and comprehension. The present paper proposes to comment on an unusual case.

First, it is generally acknowledged that 40 per cent of these tumors affect the knee and upper thigh region. The distribution, however, is not limited to any one part of the body. Rare, certainly, and probably not reported before, is a fibrosarcoma of the soft part of the finger, the thesis of this paper. Fig. 1 indicates the locations of several tumors of the hand and foot and particularly one of the small toe.<sup>2</sup> But nowhere was it possible to find in any available source of literature a tumor limited to and involving only the soft parts of the finger (Fig. 2).

This patient, a 66-year-old male, was referred to me because he had a large swelling on the middle finger of his right hand. The mass appeared foreboding, and a malignancy was suspected. A biopsy of a small section of the tumor revealed on microscopic examination (Fig. 3) a fibrogenic, fibrocellular sarcoma of moderately active malignancy, as ascertained by its abundant cellular components, numerous mitoses, and moderate collagen fiber elements. The fusiform shape of the cells, varying in size and clusterings, characterized it as fibrogenic, rather than simple cellular spindle-cell sarcoma.

The patient was advised of the prognosis and consented to an amputation of the finger at its metacarpal articulation.

This particular tumor was a lobulated, well-encapsulated structure at the very tip of the middle finger of the right hand. It did not involve the bony parts of the finger, either by invasion or by pressure changes, as confirmed by x-ray examination (Fig. 4). There was no evidence of infiltration into the surrounding soft tissues beyond the tumor capsule, in so far as the capsule was smooth and void of penetrating fascicles of tumor cells growing obliquely outward, a condition characteristic of extension. Furthermore, an enlarged epitrochlear gland removed at biopsy and studied under complete serial sectioning revealed only inflammatory changes and total absence of sarcoma or any apparent metastatic findings.

The tumor was 4 by 4 cm., only slightly tender, and painless except on accidental contact. It represented a growth of four years' duration from the date of the original injury.

This brings us to the second interesting feature of this case. Ewing<sup>3</sup> has reflected considerable doubt on the relationship of trauma as an initiating agent to the formation of a tumor. His six postulates are formidable barriers to hurdle. In this instance, however, they seem to be fulfilled.

After eliminating the 3 fatal cases with a mortality rate of 9.1 per cent, those remaining may be graded as follows: Seventeen patients, or 51.5 per cent, fall into the classification of good results at this time, and it must be taken into consideration that a number of these cases are fairly recent. Eight patients, or 24.2 per cent, at this time may be classified as fair results. It is very likely that at least one-half of these will be classified as good results within six months. Five patients, or 15.1 per cent, have disappeared so that no information concerning their present status could be obtained.

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Drainage will be in order when all signs of dehydration have been overcome, when the location of the focus can be determined with some degree of certainty, and when there is reasonable evidence that pus is present.

Come what may, the surgeon should not lose his balance and be stampeded into an inexpedient operation simply because he has a patient with septicemia who develops an abscess within the substance of bone.

ecchymosis did not resorb after several months, the patient drilled a small hole through the nail with a penknife. A serosanguinous material exuded through the hole. A few days later, some varnish remover penetrated the nail bed through this hole and caused considerable distress. The mass, however, progressively enlarged, rapidly pushing the nail from its bed. The patient later removed the nail with his own fingers. The growth finally assumed the size and proportions noticed on his first visit to the doctor's office.



Fig. 3.—Fibrogenic fibrocellular sarcoma with numerous mitotic figures and moderate collagen fibers ( $\times 200$ ).



Fig. 4.—Roentgen studies of tumor.

This patient is a well-nourished, active individual, who operates his own business as plasterer and interior decorator. While loading debris from one of the buildings onto a truck, the tail gate was accidentally closed on his finger. Immediately, considerable ecchymosis formed over the tip of the finger, especially under the nail. Several days later he noticed a small nodule developing under the nail. When the

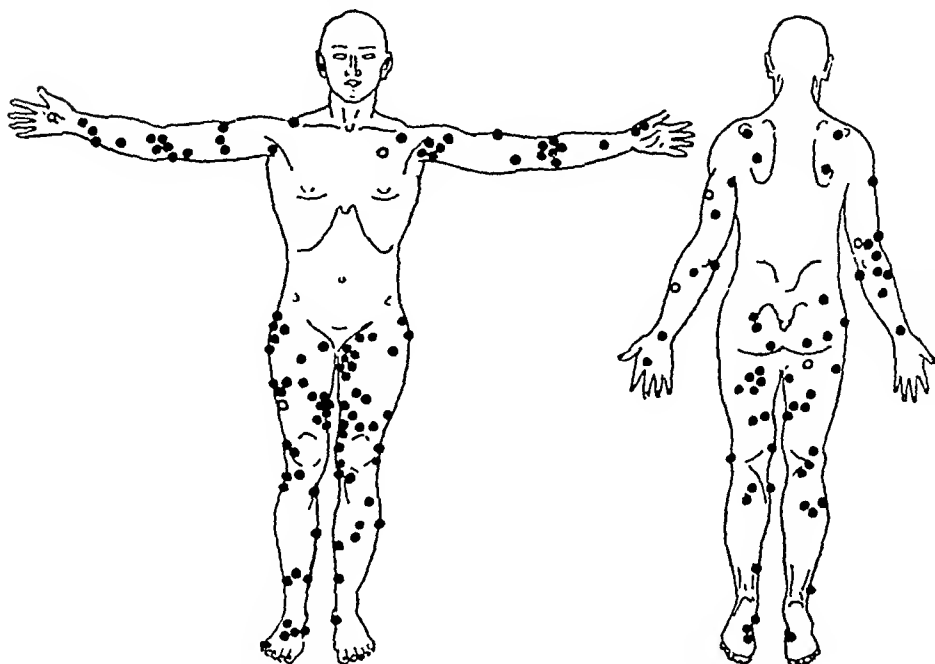


Fig. 1.—Distribution of tumor (modified after Meyerding et al.).



Fig. 2.—Tumor of the soft parts of the middle finger, right hand. Four years' growth.

# THE BLOOD SUPPLY OF THE FIRST PART OF THE DUODENUM\*

WITH DESCRIPTION OF THE GASTRODUODENAL PLEXUS

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(From the Departments of Pathology and Surgery, University of Minnesota  
Medical School)

THE BLOOD supply of the duodenum, especially that of the ulcer-bearing portion, is of great surgical importance. Its investigation has apparently received very little study. The portions of the standard surgical and anatomical textbooks devoted to the description of the blood supply of the duodenum for the most part are repetitions of earlier inadequate studies. The pattern of the gross blood supply should be restudied. With this in mind we have injected arterial specimens of the newborn and adult duodenum and have noted the rich vascular network of arteries on the posterior wall of the duodenum. This we have chosen to call the gastroduodenal plexus. A perusal of the old anatomical atlases indicates that early anatomists were familiar with the large anastomoses present on the posterior wall of the duodenum. Bougery in 1839 (Fig. 1) illustrated this plexus in a simplified manner. Poirier and Charpy in 1901 reproduced a similar drawing. The gastroduodenal plexus is worthy of further elaboration.

Bleeding peptic ulcers are often situated on the posterior wall of the first part of the duodenum. A series of short anastomosing submucosal arteries make up a well-known plexus which, if it is eroded, may give rise to hemorrhage. Severe sudden hemorrhage, however, comes from larger vessels and may come from the gastroduodenal artery itself, usually with disastrous results. Wangensteen feels that there is little likelihood of arresting bleeding satisfactorily by vessel ligation. He, therefore, has been performing gastric resection for massive hemorrhage from duodenal ulcer, excising the ulcer and closing the end of the duodenum as in the Billroth II type of resection. Bleeding from a duodenal ulcer is more frequent and usually more severe than bleeding from a gastric ulcer. Allen and Benediet in a study of 1,804 patients with duodenal ulcer treated at Massachusetts General Hospital reported that 628, or approximately one-third, had gross bleeding. Of these 40.1 per cent had minor bleeding without secondary anemia and 31.9 per cent had severe enough bleeding to produce a marked secondary anemia. In their series over 3 per cent of all patients with gross hemorrhage eventually died of hemorrhage. The mortality in sudden massive hemorrhage was 14.5 per cent regardless of treatment. Death rarely occurred

\*Awarded the Rollin E. Cutts Prize in Surgery, May, 1940, University of Minnesota Medical School.

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Practically all the surveys on the subject emphasized the nontraumatic origin of these tumors and the improbability that single trauma was capable of producing a malignant growth. True, a small percentage of patients gave a history of accident associated with tumor formation; nevertheless, on sifting the information, no convincing evidence could be brought forth to show more than an indirect etiologic relationship.

Here, however, is an authenticated case of tumor formation following a single severe injury to a healthy organ. The growth corresponded to the injured area and occurred within a reasonable time after the date of the injury. The microscopic examination of a specimen of the tumor confirmed its malignant character.

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## METHOD OF STUDY

The celloidal corrosion injection technique was readily available to me from previous studies. It is especially adaptable to this type of investigation. The developmental changes in the blood supply were studied by injecting two six-month fetuses, three newborn infants, one 5-day-old infant, and 1 adult.

The injections (Fig. 6) were all made *in situ* at post-mortem, a cannula being tied securely in the lower portion of the thoracic aorta just above the diaphragm and a ligature tied around the hepatic artery at the porta hepatis and the abdominal aorta distal to the origin of the superior mesenteric artery. Thus, the stomach, small intestine, part of the large intestine, and spleen were injected.

The celloidal corrosion injection method has been well described in the literature by many men, among them Hinman, Morison, Lee-Brown, Barker, and Pettigrew. The first step in injection involves the perfusion of water through the aorta until the return flow from the vena cava is no longer blood tinged. After the vascular system has been washed out, a celloidin-acetone-camphor solution is injected under pressure. The acetone combines with the water and the celloidin precipitates out to make a cast of the vessels. Camphor is added to make the final preparation less brittle and alkanin is used as a red dye. A 3 per cent celloidin solution is first injected under 400 mm. pressure to obtain a cast of the finer vessels; this is followed by a 10 per cent celloidin solution under 300 mm. to obtain a cast of the larger vessels. In the adult the thin solution is injected under pressure for thirty minutes, and then the thick solution is injected and kept under a constant pressure for twenty-four hours. Since the vessels are so much smaller in newborn infants and fetuses, the thin solution is injected for only ten minutes and the thick solution for one hour. During the entire injection the specimens are kept under cold running water. At the end of the prescribed time, the cast of the vessels is sufficiently set to allow corrosion.

The adult stomach and viscera were injected with a thin solution in the post-mortem room; they were then removed from the body and were injected with the thick solution in the laboratory. The newborn infants were easiest to inject since after one hour the posterior peritoneum could be stripped from the body wall and the viscera simply removed *en masse*. Due to the difficulties in obtaining and injecting adult material, we were able to obtain only one satisfactory specimen though several attempts were made; often preliminary injections had been tried on the dog.

The viscera to be corroded were placed in a bath of pure commercial hydrochloric acid and left there for twelve (newborn) or forty-eight hours (adults). At the end of this time the tissues were sufficiently cor-

from hemorrhage in patients under 50 years of age. Christopher writes that, if surgery is indicated, the operation of election is the exposure of the bleeding ulcer, the cutting off its blood supply by overlapping sutures about it, excision if feasible, and in some instances gastroenterostomy at the discretion of the surgeon.

More and more both gastroenterologists and surgeons are beginning to appreciate that conservative nonoperative management of massive hemorrhage carries a fairly high mortality, probably in the neighborhood of 10 per cent.

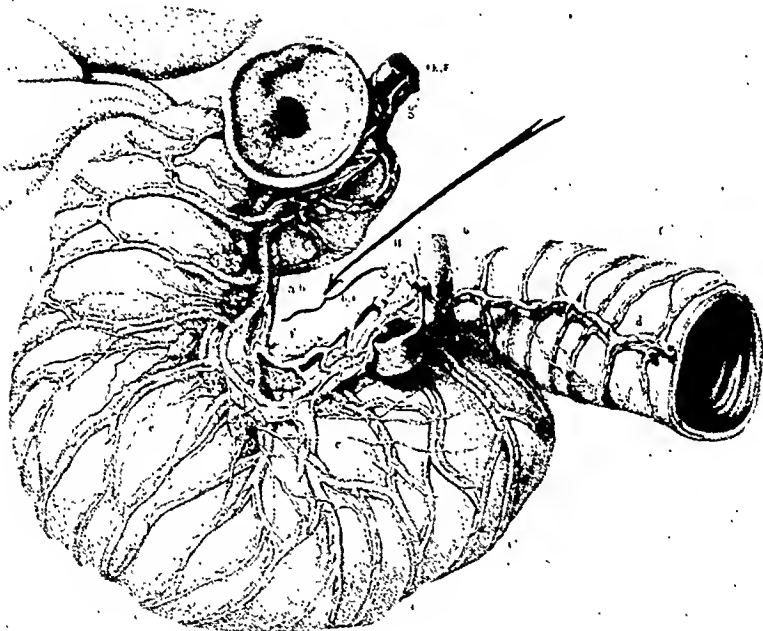


Fig. 1.—Photograph of the drawing of the blood supply of the duodenum from Bourguery's anatomical atlas published in 1839. The superior and inferior pancreaticoduodenal arteries are shown to divide into two arcades and anastomoses between them appear in the lower half. The anastomoses are not nearly as extensive or as numerous as our preparations show. Nevertheless, this is the earliest demonstration of such anastomoses that we have been able to find.

It will be seen from the following study that, while bleeding may come from erosion of the submucosal plexus, sudden severe hemorrhage may come from another plexus of larger arteries behind the posterior wall of the duodenum. This plexus is deeper (toward the retroduodenal tissues) than the submucosal vessels, and the name gastroduodenal plexus has been suggested on reviewing the material of this study. The anatomic possibilities for collateral blood flow, as observed in this study, suggest that satisfactory hemostasis is not likely to be attained by the placement of multiple ligatures, when operating for bleeding duodenal ulcer.

of the posterior wall of the first part of the duodenum. When the supraduodenal artery of Wilkie arises from the gastroduodenal artery, it usually takes the form of a short trunk which, arising on a level with the upper border of the duodenum, soon ends by dividing into a spraylike formation, the branches for the most part arching over the front of the duodenum. W. J. Mayo called attention to the anemic spot on the anterior surface of the duodenum in certain cases seen during operation when the pylorus and first part of the duodenum

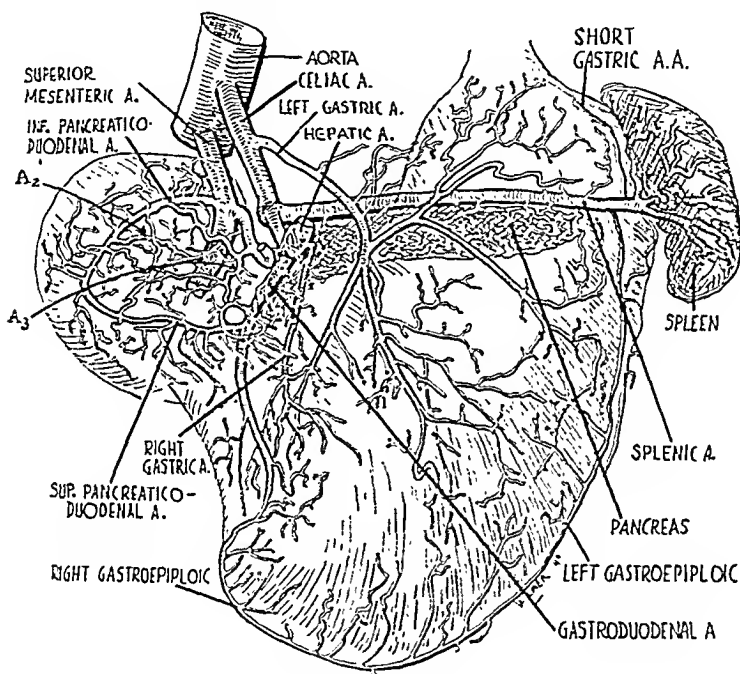


Fig. 3.—Drawing from the corrosion preparation of the arteries of the stomach and duodenum of a 5-day-old infant. The large arcade of the superior and inferior pancreaticoduodenal arteries is shown. In this case there is one main arcade. There is, however, a second anastomosis ( $A_2$ ) between this arcade and the superior mesenteric artery and a third anastomosis ( $A_3$ ) to a branch of the superior mesenteric artery. The third anastomosis ( $A_3$ ), moreover, unites in two places with the pancreaticoduodenal arcade, with the inferior mesenteric artery as well as the gastroduodenal artery. This complex anastomosing network constitutes the gastroduodenal plexus.

are pulled down at operation. Wilkie found that this spot corresponded to the area supplied by the supraduodenal artery. Wilkie noted also that branches from the pyloric artery in about 50 per cent of the cases supply the first one-half inch of the upper border and the anterior and posterior walls. The recurrent branch from either the right gastroepiploic or superior pancreaticoduodenal supplies the lower one-third of the anterior surface of the first inch of the duodenum. The retroduodenal arteries arise from the trunk of the gastroduodenal artery and supply the lower one-third of the posterior surface.

roded to be washed off. They were washed under water with a thin stream of water by means of a cannula and rubber tube connected to the faucet. The washing was carried out under a dissecting microscope, care being taken not to break the small vessel casts.

The specimens were then placed in a solution of 2 per cent formalin, 20 per cent glycerin, and distilled water. I then studied and dissected them under a binocular dissecting microscope by means of strong transillumination and drew them. Only the larger arteries and arterioles were injected at this pressure, but capillaries may be injected at a higher pressure.

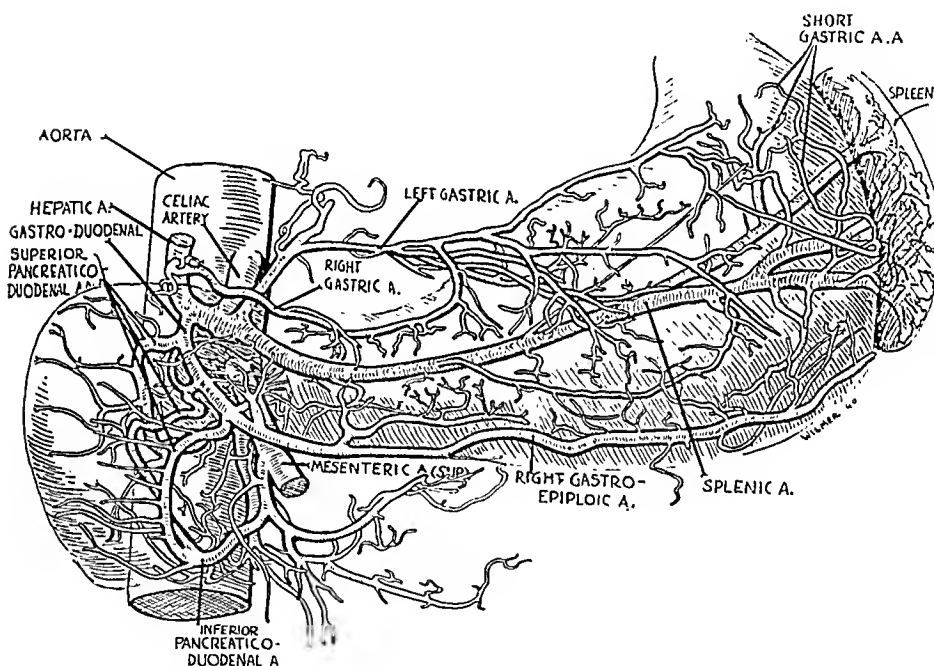


Fig. 2.—Drawing from the corrosion preparation of the arterial blood supply of the stomach and duodenum of a 6-month-old fetus. Three superior pancreaticoduodenal arteries arise from the gastroduodenal artery. The first superior pancreaticoduodenal artery unites with the upper of two inferior pancreaticoduodenal arteries, which also sends a large vessel to the third part of the duodenum. The second and third of the three superior pancreaticoduodenal arteries unite in a common vessel, the lower of the two inferior pancreaticoduodenal arteries. To arrest hemorrhage from one of these areas (the surgeon not knowing which the bleeding is coming from), it would be necessary to ligate the gastroduodenal artery and the two inferior pancreaticoduodenal arteries, thus depriving the duodenum of its blood supply. A reasonable surgical approach would be to place overlapping sutures around the bleeding ulcer.

Due to the rotation of the corrosion preparation the aorta is displaced to the right a distance approximately equal to its width.

#### BLOOD SUPPLY OF THE DUODENUM

*The Supraduodenal Artery.*—Wilkie described the supraduodenal artery which usually arises from the gastroduodenal artery but which may arise from the hepatic artery or others. It supplies the upper two-thirds of the anterior wall and the upper one-third to two-thirds

pancreatic vessels into two arcades, but usually there are actually two separate arcades, each arising from the gastroduodenal and superior mesenteric arteries respectively. In this particular specimen there was a third superior pancreaticoduodenal artery arising from the gastroduodenal artery which united with the second inferior pancreaticoduodenal artery. In Fig. 3 (5-day-old infant) there is one large pancreaticoduodenal arcade, but there are numerous anastomoses between this large arcade and several small arcades. This anastomosing plexus constitutes the gastroduodenal plexus. Large arteries of approximately the same caliber as the pancreaticoduodenal artery form this plexus

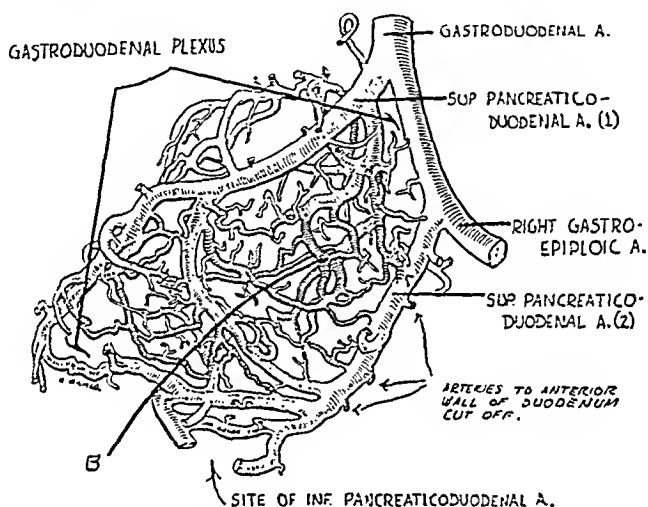


Fig. 5.—Drawing of the arteries of the posterior wall of the first part of the duodenum of a newborn infant. The arching vessels around and above the duodenum have been cut off with fine scissors under the dissecting microscope. This picture shows the gastroduodenal plexus in detail. There are two superior and two inferior pancreaticoduodenal arteries. These vessels are united across the posterior wall of the duodenum in at least six places and these six anastomoses are united among themselves in at least a dozen major points. The vessels are large in most instances and the futility of trying to ligate vessels for bleeding ulcer is readily seen. In order to arrest bleeding from an arbitrary point marked *B* on the drawing it would be necessary to ligate no less than nine vessels which extend all along the first part of the duodenum. With even the greatest amount of skill and luck it would be futile to consider the desirability of such a procedure.

and run for relatively long distances posterior to the duodenum. Erosion of any of these anastomosing vessels would be almost as severe as erosion of the pancreaticoduodenal artery. Fig. 4 (adult) shows the gastroduodenal plexus best. Here there are two large arcades of pancreaticoduodenal arteries, one on each side of the duodenum, and between them are seen large anastomosing vessels, which are united by smaller anastomosing vessels (the gastroduodenal plexus). The vessel coming off of the terminal portion of the gastroduodenal artery and dividing like a spray may be the supraduodenal artery, but, since the duodenum was brought up above the stomach and turned to show the gastroduodenal plexus, the relations at the pylorus were lost. It is

*The Pancreaticoduodenal Arteries.*—Except for this first one and one-half inches the duodenum receives all its blood supply from the pancreaticoduodenal arteries. The superior and inferior pancreaticoduodenal arteries divide into two branches, forming two arcades which send off vessels to the duodenum which tend to encircle the bowel.

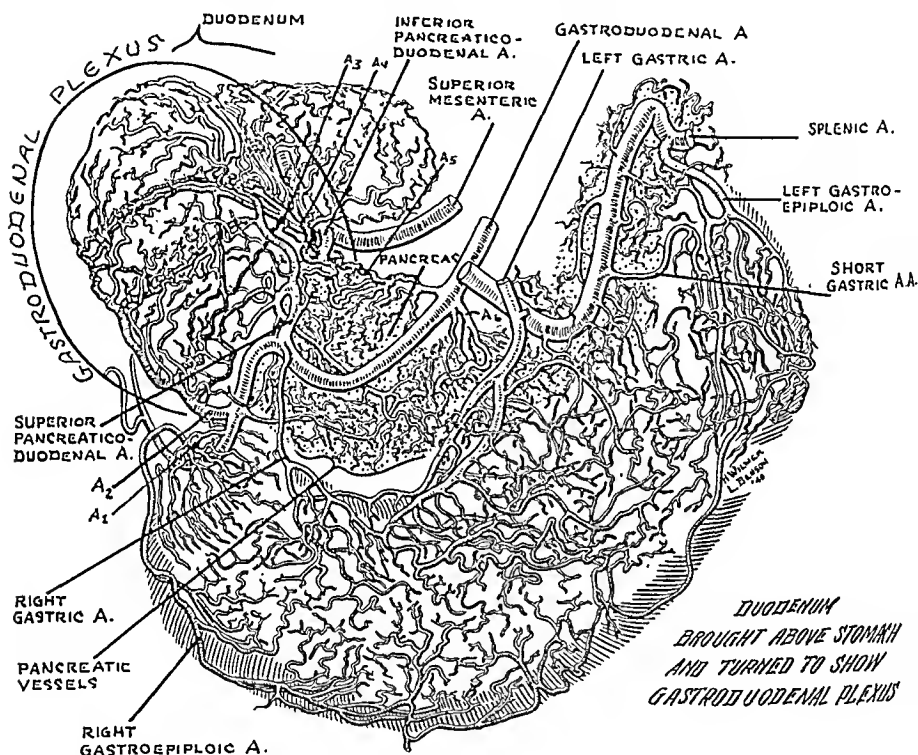


Fig. 4.—Drawing from the corrosion preparation of the arteries of the stomach, first part of the duodenum, and the pancreas in an adult. The gastroduodenal artery gives rise to the superior pancreaticoduodenal artery which unites with one of the branches ( $A_1$ ) of the inferior pancreaticoduodenal artery. A second large branch of the gastroduodenal artery forms the superior branch of ( $A_2$ ) a second pancreaticoduodenal arcade by uniting with a branch ( $A_3$ ) of the inferior pancreaticoduodenal artery. The gastroduodenal artery is further united with the inferior pancreaticoduodenal artery by an anastomosis ( $A_5$ ). Smaller connections between the various branches of the gastroduodenal artery are seen ( $A_6$ ). Numerous fairly large vessels (shaded darkly) will be seen uniting all of these arcades and anastomosis. These arcades and anastomoses on the posterior wall of the duodenum constitute the gastroduodenal plexus. Due to the fact that the duodenum was brought above the stomach and turned to show the plexus, there is some question as to whether  $A_1$  represents the supraduodenal artery or not.

They soon pierce the muscular coats and form a submucosal plexus of anastomosing vessels which are short and relatively of the same length and caliber.

*The Gastroduodenal Plexus.*—Quite aside from these short anastomosing vessels forming the submucosal plexus, there is another plexus of very large vessels which we have been able to identify in our preparations. Fig. 2 shows a drawing of the vessels of the 6-month-old fetus. There may be a simple branching of the superior and inferior

pancreatic vessels into two arcades, but usually there are actually two separate arcades, each arising from the gastroduodenal and superior mesenteric arteries respectively. In this particular specimen there was a third superior pancreaticoduodenal artery arising from the gastroduodenal artery which united with the second inferior pancreaticoduodenal artery. In Fig. 3 (5-day-old infant) there is one large pancreaticoduodenal arcade, but there are numerous anastomoses between this large arcade and several small arcades. This anastomosing plexus constitutes the gastroduodenal plexus. Large arteries of approximately the same caliber as the pancreaticoduodenal artery form this plexus

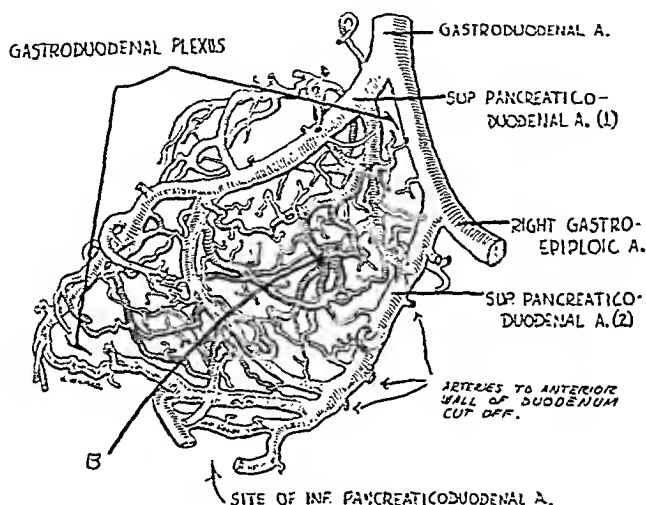


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to be remembered that the drawings were made from casts and that all the tissue of the stomach and duodenum was corroded away. Small branches from the gastroduodenal plexus supply the posterior wall of the first part of the duodenum.

Fig. 5 shows in detail the arrangement of the gastroduodenal plexus. The small vessels and the vessels arching around the walls of the duodenum have been dissected off with fine scissors, so that only the vessels of the posterior wall of the duodenum are shown.

It is certain that variations are the rule in vascular anatomy and that the vessels to the duodenum are not constant and represent only a relatively constant pattern of pancreaticoduodenal arcades and anastomoses. All anastomoses and gastroduodenal plexuses vary in pattern, but it is certain that their presence has been clearly demonstrated. The gastroduodenal plexus is made up of vessels which begin and end in large vessels and, though their branches may be terminal, they are not.

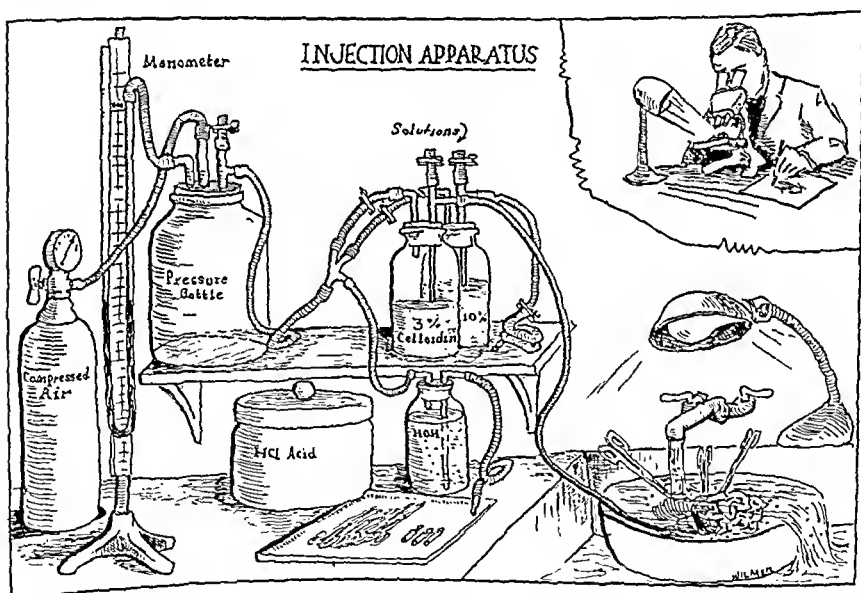


Fig. 6.—Drawing of the injection apparatus used, with an insert showing the method of study with a dissecting microscope.

#### CONCLUSIONS

The most important point in the understanding of the blood supply of the duodenum is its variations in pattern, at least of the larger vessels. There are usually two pancreaticoduodenal arcades. Uniting these arcades are large anastomosing vessels running for a relatively long course on the posteromedial wall; they, in turn, are united by smaller anastomosing vessels; these anastomosing vessels constitute the gastroduo-

denal plexus. It is not the same as the submucosal plexus of smaller, shorter vessels which on the posterior wall arise from branches of the gastroduodenal plexus. Erosion of one of these large posterior vessels of the plexus probably causes sudden severe hemorrhage, as compared to the constant slow hemorrhage due to erosion of the submucosal vessels.

The complexity of the gastroduodenal plexus suggests that it is unlikely that vessel ligation will suffice to control bleeding in massive hemorrhage from a posterior wall duodenal ulcer.

I am indebted to Dr. Owen H. Wangensteen for the suggestion of this study, to Dr. E. T. Bell for the opportunity to execute it, and to Dr. R. E. Scammon for anatomical criticisms. I am also grateful for the helpful cooperation of Dr. Harriet Mitchell and Dr. Carl Lind in obtaining post-mortem material, and to Lawrence Benson for artistic assistance in drawing Fig. 4.

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## REPEATED PERFORATIONS OF PEPTIC ULCERS

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IT IS difficult to estimate accurately from the literature the exact incidence of repeated perforations of peptic ulcers. It would undoubtedly be true that a complete review of all the papers on perforated ulcer would show that this complication is more frequent than the few cases reported in the literature would lead one to believe. Gosset and co-workers<sup>1</sup> in 1938 were only able to find 64 cases. They added 2 additional cases. Since this review Grizzard<sup>2</sup> has reported 1 case, Bottin<sup>3</sup> has reported 3 cases, and Ross and LeTourneau<sup>4</sup> in their review of perforated ulcers mentioned that they had had 4 cases of repeated perforations. Four cases are described in the American literature which have not been mentioned by Gosset and his associates. Pearse<sup>5</sup> found 33 cases of recurrent perforations in a series of 4,813 patients with perforated ulcer, an incidence of 0.69 per cent. He also observed that the mortality rate in this group was lower than that for perforated ulcer as a group, presumably because the previous experience had taught the patient to consult the surgeon at once and because of the local reaction of the peritoneum.

The accident of repeated perforation of the same ulcer must be distinguished from that of perforation of more than one ulcer in the same patient. This, also, must be more common than the literature would indicate. Masson and Simon<sup>6</sup> in 1927 collected only 33 cases. The frequency of kissing ulcers is well known. Lewisohn<sup>7</sup> found that in his gastrectomy specimens 50 per cent had two or more ulcers. Graves<sup>8</sup> reported that the German surgeons estimated that 20 to 50 per cent of all ulcers were multiple. It is interesting that the mortality rate for multiple perforations is much higher than the rate for repeated perforations of the same ulcer. Pearse calculated the mortality rate of patients having repeated perforations to be 4 per cent, while in those cases of multiple perforations reported by Masson and Simon there were 23 fatalities in the group of 33 patients.

Both groups of cases are of interest in regard to the clinical impression that perforation of an ulcer is really a blessing in disguise in that it very often results in a cure of the ulcer. The surgical procedure of cautery excision of the ulcer probably owes its origin to this belief. As has been frequently pointed out, this assumption is not warranted. Grey-Turner estimated that only 50 per cent of patients with perforations were cured by the perforation. Lewisohn found that 39 per cent

of his patients had persistence of symptoms. Sullich reported that 70 per cent of his patients were not cured by perforation.

The experience at the San Francisco Hospital, a large city hospital, would seem to agree with a high incidence of persistence of symptoms. Since there is no out-patient department except for immediate post-operative care, no accurate estimate can be made. That a group of patients of the type treated in a large city hospital might be expected to have a higher incidence of persistence of symptoms is obvious. None of the patients reported in this small series followed their dietary regimen for more than a short time. In fact, the perforation usually occurred followed a dietary indiscretion, usually alcoholic.

From January, 1935, to June, 1940, there have been 12 cases of reperforation of peptic ulcers at the San Francisco Hospital. During this time there have been 300 perforations repaired. Rhodes and Collins,<sup>9</sup> reporting on 155 consecutive perforations from this hospital up to 1933, found a mortality rate of 25 per cent. They observed that, if those patients reporting to the emergency service later than ten hours after perforation were excluded, for 117 operations the mortality was 13 per cent. In the past five years the mortality rate on all operated cases of perforated ulcer has fallen to 15 per cent. This improvement in a large part seems due to the increased efficiency of the emergency hospital service permitting prompt operation.

The type of surgical therapy to be instituted is a matter of debate. Most surgeons believe that for the initial perforation simple closure with reinforcement with omentum is the simplest and safest procedure. If there is a high degree of pyloric obstruction, a gastroenterostomy may be necessary. There are those who advocate a primary gastric resection if the patient is operated upon early enough after the perforation and is in good enough condition. Judin<sup>10</sup> reported a mortality rate of only 12.8 per cent in 426 primary resections.

A posterior gastroenterostomy was performed in only one patient in this group. This operation was performed following his third perforation (Case 8). He remained symptom free for ten years before his disease recurred. Most of the cases in the literature have gone through the sequence of repeated perforations with simple closure, then gastroenterostomy, finally gastric resection. The gastroenterostomy did nothing to prevent the reperforation. In fact it simply made the eventual resection more difficult, due to the development of marginal ulceration. The interesting cases of Davenport,<sup>11</sup> Butler,<sup>12</sup> and Lysaght and Wilkans<sup>13</sup> illustrate this point. Finsterer<sup>14</sup> states that, in the presence of a perforation of a chronic ulcer which has simply been closed due to the condition of the patient, he advises the patient to return in three months for a gastric resection whether he is symptom free or not. He regards a gastroenterostomy as an operation to be performed in unusual instances.

It would seem wiser then, when faced with the choice of operation in a patient with repeated perforation, either simply to close the ulcer, or, if the patient's condition warrants, to perform a gastric resection. If the patient's condition is bad, or if several hours have elapsed since the perforation, it might be wiser to do a simple closure, followed by a gastric resection after recovery from the operation. Unless a high degree of pyloric stenosis is present, a gastroenterostomy should not be done.

Twelve cases of repeated perforations of peptic ulcers are reported.

#### CASE REPORTS

CASE 1.—(D159133.) A 34-year-old American laboring man entered the hospital on Nov. 16, 1935, with a three-hour story of sudden onset of acute epigastric pain which rapidly became generalized. Six years before the patient had had a similar attack. At that time a perforated ulcer at the pylorus was found and closed at St. Luke's Hospital in San Francisco. Following his first operation he remained on a diet for two months. He was symptom free for two years. Then he began to have eructations of gas and fleeting epigastric pains.

On entry he was found to have generalized abdominal tenderness with upper abdominal rigidity and spasm. W.B.C., 14,100; urine, negative. A flat abdominal x-ray showed gas under the diaphragm.

At operation cloudy, bile-stained fluid was found in the abdomen. An acute ulcer was found just on the gastric side of the pylorus on its anterior surface. No adhesions were described in the operative note. The ulcer was closed with interrupted stitches, and tags of omentum were sewed over it.

The postoperative course was uneventful.

CASE 2.—(D131128.) A 36-year-old American laborer entered the hospital on Aug. 20, 1933, ten hours after the onset of severe abdominal pain. Five years before the patient had had a similar attack which cleared up spontaneously in a few weeks. Six weeks before entry he began to have epigastric pains occurring a few hours after meals. These were relieved by soda and vomiting. The day before entry the patient had had "a few drinks."

On entry he was found to have a rigid, tender abdomen. W.B.C., 22,000; urine, three-plus sugar and trace of acetone. A flat x-ray of the abdomen showed no free gas.

Under spinal anesthesia the abdomen was opened and a perforated duodenal ulcer found which was covered with omentum. A second ulcer crater was noted on the posterior wall of the stomach. The ulcer was closed with interrupted stitches and the omentum sewed over it.

The patient re-entered the hospital Aug. 14, 1934, with a similar attack of pain of five hours' duration. His symptoms had completely returned three months before the second entry. W.B.C., 26,000; urine again showed sugar and a trace of acetone. Blood sugar, 117 mg. per cent. A flat abdominal x-ray showed free gas under the diaphragm.

At the second operation a perforation was found on the anterior surface of the duodenum just proximal to the old operative site. The ulcer was again closed and covered with omentum.

The patient re-entered a third time Feb. 15, 1935, with a recurrence of his symptoms. At this entry he was relieved on a rigid medical regimen.

CASE 3.—(D165693.) A 28-year-old Chinese house boy was in the surgical ward for the treatment of osteomyelitis of the left femur. On April 4, 1936, he had an

attack of severe right upper quadrant pain associated with nausea and vomiting. Further questioning showed that he had had similar attacks in the past. Examination showed upper abdominal tenderness and spasm. A flat abdominal x-ray showed free gas under the diaphragm.

Under spinal anesthesia the abdomen was opened and a 5 mm. perforation found in the duodenum on its anterior aspect. The ulcer was excised and closed and omentum sewed over the area.

The patient re-entered June 7, 1940, with sudden severe pain which caused him to collapse five hours before entry. He had not been on a diet and had been having "stomach trouble" since a few months after his first abdominal operation. Examination again revealed signs of peritonitis. A flat abdominal x-ray showed free gas under the diaphragm. W.B.C., 16,000; urine, negative.

At operation the same ulcer was found to have re-perforated. A simple closure of the ulcer was done.

CASE 4.—(D170332.) A 39-year-old laborer entered with a story of severe abdominal pain nine hours before entry, followed by nausea and vomiting. He had had "stomach trouble" for four years. Examination showed signs of peritonitis. W.B.C., 15,640; urine, negative. An x-ray of the abdomen showed free gas. At operation an ulcer on the anterior surface of the pylorus was found and closed.

Fifteen months later the patient re-entered for treatment of a urethral abscess. At this time he was having all his old symptoms again, especially after a drinking bout.

Two months later he again re-entered with severe abdominal pain of two hours' duration. Examination showed signs of peritonitis. W.B.C., 16,000; urine contained sugar and acetone. An abdominal x-ray showed free gas under the diaphragms.

Postoperatively the patient developed delirium tremens. On the third day he became eviscerated after getting out of bed. He died two days later.

CASE 5.—(D125196.) A 27-year-old laborer entered Feb. 4, 1933, with a twelve-hour history of generalized abdominal pains radiating to the right shoulder associated with nausea and vomiting. The patient had had two similar bouts of pain in the past. In one of these attacks his appendix had been removed at another hospital. On examination he had spasm and tenderness in the upper abdomen. A flat x-ray of the abdomen showed free gas under the left diaphragm. The patient refused surgery as he felt he was improving.

The localized peritonitis gradually subsided. A gastrointestinal series showed a duodenal ulcer.

He re-entered Nov. 28, 1936, with a similar attack of five hours' duration. His vague symptoms had begun again three months before entry. Examination again showed free gas under the diaphragm along with the clinical picture of a general peritonitis. W.B.C., 13,000; urine, negative.

At operation many old and new adhesions were found between the pylorus and undersurface of the liver. The pylorus was scarred. A perforation was found on the anterior surface of the duodenum. It was a large ulcer and there was a kissing ulcer on the posterior surface of the duodenum. The ulcer was split and the defect closed transversely.

The patient again re-entered with a recurrence of symptoms on Dec. 10, 1937. On a strict dietary regimen the symptoms improved.

CASE 6.—(D166526.) A 49-year-old American butcher entered May 27, 1936, with a ten-hour history of sudden onset of severe abdominal pain associated with nausea and vomiting. The patient had had two previous entries for renal stones, for which he eventually had a nephrectomy. Examination revealed signs of a generalized peritoneal irritation. Air was seen under both diaphragms in the x-ray.

It would seem wiser then, when faced with the choice of operation in a patient with repeated perforation, either simply to close the ulcer, or, if the patient's condition warrants, to perform a gastric resection. If the patient's condition is bad, or if several hours have elapsed since the perforation, it might be wiser to do a simple closure, followed by a gastric resection after recovery from the operation. Unless a high degree of pyloric stenosis is present, a gastroenterostomy should not be done.

Twelve cases of repeated perforations of peptic ulcers are reported.

#### CASE REPORTS

CASE 1.—(D159133.) A 34-year-old American laboring man entered the hospital on Nov. 16, 1935, with a three-hour story of sudden onset of acute epigastric pain which rapidly became generalized. Six years before the patient had had a similar attack. At that time a perforated ulcer at the pylorus was found and closed at St. Luke's Hospital in San Francisco. Following his first operation he remained on a diet for two months. He was symptom free for two years. Then he began to have eructations of gas and fleeting epigastric pains.

On entry he was found to have generalized abdominal tenderness with upper abdominal rigidity and spasm. W.B.C., 14,100; urine, negative. A flat abdominal x-ray showed gas under the diaphragm.

At operation cloudy, bile-stained fluid was found in the abdomen. An acute ulcer was found just on the gastric side of the pylorus on its anterior surface. No adhesions were described in the operative note. The ulcer was closed with interrupted stitches, and tags of omentum were sewed over it.

The postoperative course was uneventful.

CASE 2.—(D131128.) A 36-year-old American laborer entered the hospital on Aug. 20, 1933, ten hours after the onset of severe abdominal pain. Five years before the patient had had a similar attack which cleared up spontaneously in a few weeks. Six weeks before entry he began to have epigastric pains occurring a few hours after meals. These were relieved by soda and vomiting. The day before entry the patient had had "a few drinks."

On entry he was found to have a rigid, tender abdomen. W.B.C., 22,000; urine, three-plus sugar and trace of acetone. A flat x-ray of the abdomen showed no free gas.

Under spinal anesthesia the abdomen was opened and a perforated duodenal ulcer found which was covered with omentum. A second ulcer crater was noted on the posterior wall of the stomach. The ulcer was closed with interrupted stitches and the omentum sewed over it.

The patient re-entered the hospital Aug. 14, 1934, with a similar attack of pain of five hours' duration. His symptoms had completely returned three months before the second entry. W.B.C., 26,000; urine again showed sugar and a trace of acetone. Blood sugar, 117 mg. per cent. A flat abdominal x-ray showed free gas under the diaphragm.

At the second operation a perforation was found on the anterior surface of the duodenum just proximal to the old operative site. The ulcer was again closed and covered with omentum.

The patient re-entered a third time Feb. 15, 1935, with a recurrence of his symptoms. At this entry he was relieved on a rigid medical regimen.

CASE 3.—(D165693.) A 28-year-old Chinese house boy was in the surgical ward for the treatment of osteomyelitis of the left femur. On April 4, 1936, he had an

and he was gradually losing ground because of constant vomiting. A gastrointestinal series showed a duodenal niche but no gastric retention. A gastric resection was advised.

At operation many adhesions were found. There was a large mass in the region of the duodenum. When freed, the duodenum was seen to be completely transected except for the mucous membrane on the posterior wall. The two ends opened into an abscess cavity the size of a fist.

A wide gastric resection was done with a posterior Pólya anastomosis. At first the patient did well. After the stomach tube was removed, he had difficulty in swallowing. Barium demonstrated spasm at the junction of the middle and distal thirds of the esophagus. This seemed to improve with belladonna and the patient was discharged on a strict diet.

He was brought in June 21, 1940, in extremis from starvation. At autopsy a large shallow ulcer of the esophagus was found at the site of the spasm. The stomach had healed well.

CASE 11.—(D219703.) A 56-year-old white male WPA worker entered Jan. 2, 1939, with a complaint of dull epigastric pain of eighteen months' duration. The onset had been rather sudden with a bout of fainting followed by passage of several large black stools. Since then he would have bouts of pain lasting four to five days and then be relatively free of symptoms. About two weeks before entry he began vomiting daily. He had lost 15 pounds in weight. On entry his physical examination revealed nothing. R.B.C., 5,130,000. No blood present in the stool. A gastrointestinal series showed a duodenal ulcer. He was placed on the Sippy regimen.

He re-entered six months later. He had not been improved by his diet and a repeated gastrointestinal series showed no change in the size of the ulcer. He was again discharged.

On Sept. 16, 1939, two hours before entry the patient had been seized with a severe epigastric pain radiating throughout the abdomen. Examination showed a boardlike abdomen. W.B.C., 9,200. A flat abdominal x-ray showed free gas under the diaphragm.

At operation a perforated anterior duodenal ulcer was found. This was closed with interrupted inverting sutures and reinforced with omentum. He recovered uneventfully from the operation and was again discharged on a dietary regimen.

Feb. 24, 1940, he again re-entered with severe abdominal pain of four hours' duration. He had only been "fairly well" since his last entry, even though he had stayed on his diet.

Examination revealed signs of peritonitis. Urine, negative; W.B.C., 13,200. X-ray showed free gas under the diaphragm.

At operation a perforation was found adjacent to the site of the previous perforation. This previous perforation was identified by the scarring in the duodenum. The perforation was closed with interrupted stitches and reinforced with omentum. The patient recovered uneventfully.

CASE 12.—(D211983.) A man, 54 years of age, entered Aug. 20, 1939, because of abdominal pain of seven hours' duration. For two to three years he had been having vague epigastric pains relieved by food and soda. The pains became quite strong and constant about three days before entry and he vomited several times.

Examination showed tenderness and spasm in the upper abdomen. W.B.C., 20,600; urine, negative; few R.B.C. casts. No free air was seen on the flat abdominal x-ray.

At operation an ulcer was found to have perforated on the gastric side of the pylorus and to have been sealed off with omentum. It was closed with interrupted stitches and reinforced with omentum. His postoperative course was uneventful.

On Feb. 13, 1940, the patient re-entered. He had been asymptomatic even though he had not been on a diet since his last operation. However, three days

At operation a perforation was found on the anterior wall of the duodenum. This was sutured transversely and closed.

The patient re-entered Jan. 23, 1937, with a similar history of seven hours' duration. He had been symptom free while on his diet, but he had stopped the diet three months after his discharge from the hospital. All his symptoms had then returned. Examination again showed signs of peritonitis. The x-ray revealed free air under the diaphragm. At operation the same ulcer had re-perforated. There were a few old adhesions present. The edges of the ulcer were excised and the ulcer was closed. Omentum was sutured over it.

CASE 7.—(D149153.) A 20-year-old laborer entered Jan. 21, 1935, with a seven-hour history of sudden severe epigastric pain. Seven to eight months before entry he had begun to have vague epigastric distress associated with eating and relieved by soda. Three days before entry the pain became much worse. Examination showed generalized spasm and tenderness. W.B.C., 11,000; urine, negative.

At operation a perforation of a gastric ulcer near the pylorus on the greater curvature was found. This was closed with mattress stitches.

The patient re-entered Feb. 19, 1938. He had been symptom free for six months following the operation. Then his discomfort returned. Two hours before entry he had another sudden very severe abdominal pain. In spite of signs of generalized peritonitis his W.B.C. was again low, 7,800 and no air was seen by x-ray.

At operation a large amount of stomach contents was found in the free peritoneal cavity. A perforation was found on the anterior surface of the duodenum just at the pylorus. There were firm omental adhesions in the region of the ulcer. Apparently the previous ulcer had been just above the present ulcer. No kissing ulcers were seen. The ulcer was closed and an omental tab sewed over it.

CASE 8.—(D68269.) A 47-year-old American laborer entered March 5, 1928, with a complaint of abdominal pains of three days' duration. He had been well up to the time the pains began. Just before entry the pain became especially severe. He had vomited three times. On entry he was found to have signs of generalized peritonitis. W.B.C. 25,000; urine, negative.

At operation a perforation was found on the lesser curvature of the stomach near the pylorus. The perforation was covered with fibrin. It was inverted with a pursestring stitch and omentum sewed over the site.

The patient re-entered Oct. 25, 1928, stating that he had been symptom free until one hour before entry. At that time he had a very severe epigastric pain. He had signs of a local peritonitis. W.B.C. 29,000; urine, negative.

At operation very little fluid was found. The perforation was obscured by adhesions, apparently following the first operation. It seemed as if the same ulcer had perforated. The ulcer was 2 cm. in diameter. It was again simply closed.

He again re-entered Feb. 4, 1929, with a third perforation. The pain had begun again only one hour before entry. At operation many adhesions were found. The perforation was described as being in the anterior surface of the duodenum. At this time the ulcer was closed and a posterior gastroenterostomy done.

The patient re-entered a fourth time May 9, 1929, because of recurrence of his symptoms. He had not remained on a diet. When he was placed on a strict diet, he signed his release.

CASE 9.—(D223467.) A man, 47 years of age, entered April 27, 1940, with a complaint of epigastric pain and vomiting of four months' duration. On Sept. 8, 1931, he had had a perforated duodenal ulcer sutured at this hospital. His symptoms had recurred soon after the operation and again on Dec. 6, 1939, a second perforation of the duodenum had been sutured. His pains had continued unabated

## EXPERIMENTAL STUDIES ON ALIMENTARY AZOTEMIA

I. ROLE OF BLOOD ABSORPTION FROM THE GASTROINTESTINAL TRACT\*  
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SINCE the report by Sanguinetti,<sup>1</sup> in 1934, of azotemia occurring in nine cases of peptic ulcer hemorrhage, several papers have appeared and several theories have been advanced in explanation of this syndrome.

The present studies were made (1) to show that such azotemia can occur in experimental animals and (2) to attempt to explain the mechanism of the syndrome. This latter point is of especial importance from the practical standpoint because in some cases the azotemia has been offered as evidence for such disturbed liver and renal function that operation has been deemed contraindicated. If, on the other hand, the phenomenon is merely due to absorption of lost blood or some other simple mechanism, it should not be a contraindication to operation.

### REVIEW OF LITERATURE

In nine cases of hemorrhage from gastric and duodenal ulcers, Sanguinetti,<sup>1</sup> as stated above, observed increased blood urea values. These were caused, he assumed, partly by an increased destruction of protein in the body and partly by the resorption of the large quantities of blood accumulated in the intestines. In keeping with this view he succeeded in a few experimental cases in obtaining increased blood urea values subsequent to oral administration of blood in normal human beings and in guinea pigs. It is of interest that his experimental rises were much smaller than his observed clinical ones. This can partly be explained by the fact that he took readings only every twenty-four hours and thus undoubtedly missed the peak of the rise in his experiments. He stated: "*El aumento de la úrea sanguínea se debe en estos caso a la absorción intestinal de considerable cantidad de proteínas*" ("the augmentation of the blood urea was due in our cases to the intestinal absorption of a considerable quantity of protein") and also to augmentation of general metabolism and to chloropenia.

In 1935 Christiansen<sup>2</sup> described two cases of uremia following gastric hemorrhage and thought the condition arose from toxic action of the blood in the intestinal canal. Christiansen concluded that, while a few of the late deaths following bleeding ulcer are due to such complications as peritonitis in a majority of cases from perforation, embolism, pneumonia, etc., the fatal outcome results from what he called "*exhaustio virium*."

\*A portion of the thesis submitted by C. Frank Chunn to the Graduate School of the University of Michigan in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

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before entry he began to vomit. Four hours before entry he had a severe epigastric pain which had been constant up to the time of entry. He was found to have a boardlike abdomen. W.B.C., 28,500. Again no gas was seen by x-ray.

At operation only a few adhesions were present. An ulcer on the gastric side of the pylorus, apparently the same ulcer, had perforated. The pylorus appeared markedly stenosed. A gastric resection with a posterior Pólya anastomosis was done. The patient recovered and was discharged March 9, 1940.

When last seen on April 13, 1940, he had no complaints.

#### SUMMARY

1. In this series repeated perforations of peptic ulcers have occurred in 4 per cent of 300 patients operated upon for perforated peptic ulcer.
2. A radical gastric resection may offer these patients the best prognosis.

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ially likely since these latter were increased due to toxic destruction of proteins and because of dehydration.

Glass<sup>6</sup> in 1932 produced hypochloremia in dogs, at the same time preventing dehydration and starvation. These studies revealed no notable increase of nonprotein nitrogen content of the blood except immediately before death, although the loss of chlorides proceeded rapidly to one-half the normal chloride level. Glass also found that when the loss of chloride was 30 per cent or more the urine and stools contained more nitrogen than was present in the ingested food. From this he concluded that chloride deprivation causes destruction of protein, but by adequate diuresis all of the waste nitrogen is excreted. However, in about twenty days the urinary volume of his animals diminished, the nonprotein nitrogen content of the blood increased rapidly and the dogs died. Glass assumed that the marked decrease of electrolytes must have led to this diminished diuresis as there was no dehydration at all in these experiments. By giving large amounts of sodium chloride he could combat the uremia.

Sučić<sup>7</sup> in 1935 reported elevation of the urea content of the blood in 6 of 7 patients with hematemesis and melena. Five of these had duodenal ulcer, 1 a gastric ulcer, and 1 cirrhosis of the liver. In investigating this, he fed 500 and 1,000 Gm. of calves' blood respectively to 2 patients and found no increase in the blood urea content one and two days later. He also observed no increase of blood urea in 5 patients with hemoptysis, not any in 2 patients starved for three days, and none in a professional donor after the withdrawal of 600 c.c. of blood. He stated that the condition is not due to dehydration, because it can develop in the presence of adequate fluid intake.

Seliff and Stevens<sup>8</sup> in 1939 in a report of 7 cases of hemorrhage into the gastrointestinal tract in which death followed determined the blood urea nitrogen values within the first three days of the hemorrhage. In 4 cases values for blood urea nitrogen were 50 to about 105 mg. per cent; "in all of these there was repeated hemorrhage, and varying amounts of blood were found in the gastrointestinal tract in the three in which autopsy was done." In the fifth case, also with "repeated hemorrhage," the blood urea nitrogen decreased from about 42 to about 33 mg. per cent. In the sixth case in which bleeding was due to an aortic aneurysm which had ruptured into the esophagus followed by profuse hematemesis, the blood urea nitrogen remained in the vicinity of 16 to 17 mg. per cent until death. It is interesting to note that in this case "there was practically no old blood in the intestinal tract." This tends to confirm the theory that the prerequisite for the development of azotemia is the presence of blood in the intestinal tract. In Seliff's seventh case, in which bleeding had preceded admission to the hospital and none occurred during hospitalization, the blood urea nitrogen advanced from

On the basis of his observations he postulated that: "This so-called '*exhaustio virium*' covers actually a condition of extrarenal hyperazotaemia, which may be preceded and accompanied by achloruria, and that this condition may be treated successfully by administration of sodium chloride. . . . The theory is advanced that in these cases the hyperazotaemia is a symptom of an intoxication arising from absorption of toxic substances that are formed by bacterial decomposition of the blood stagnating in the intestinal canal, and that this intoxication is further aggravated by demineralization from excessive flushing of the organism by water."

Meyler<sup>3</sup> opposed this theory and experimenting with guinea pigs found dehydration an important factor after bleeding the pigs 8 to 13 c.c. of blood every two days for several days with a resultant state of "uremia" within four or five days. The sodium chloride concentration of the blood in all cases was at a normal level or slightly increased. If, however, he gave 50 c.c. of saline solution daily to the guinea pigs, the diuresis increased and a maximum negative nitrogen balance was present. The animals survived and did not show an increase of blood urea concentration.

Meyler stated that starvation also plays a role similar to dehydration in the development of extrarenal uremia, for in starvation the body lives on its own substance. As proof of this, he starved a guinea pig for three days but gave 20 c.c. of saline solution subcutaneously daily. This resulted in an increase in hemoglobin from 88 to 113 per cent and in blood urea from 40 to 130 mg. per cent. It would seem that the above experiment would indicate dehydration and associated blood concentration as the primary factor, with starvation playing a more minor role.

In 1936 Alsted<sup>4</sup> reported 26 cases suffering from hematemesis and melena originating from gastric or duodenal ulcer, esophageal varices, and carcinoma of the gastrointestinal tract. He found blood urea values of 50 mg. per cent and above in 13 of the 26 patients; 9 showed a highest value between 39 and 50 mg. per cent; in 4 patients only did he observe blood urea values below 39 mg. per cent. The renal function was determined in 4 patients with increased blood urea and no reduction of kidney function was found. He, therefore, assumed that the increase of blood urea in these cases was caused by resorption of blood in the intestine and by dehydration of the tissues.

In 1936 Meyler<sup>5</sup> in a second paper on "Uraemia Due to Dehydration" reported an experiment in which the blood urea content of a guinea pig was increased from 45 to 197 mg. per cent in a six-day period, during which time the animal was dehydrated. The renal function remained unimpaired until the sixth day. He concluded that the functional renal impairment due to low blood pressure caused by dehydration and subsequent decreased circulating blood volume, was such that the kidneys were unable to carry off the nitrogenous waste products. This was espe-

cially likely since these latter were increased due to toxic destruction of proteins and because of dehydration.

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40 to 52 mg. per cent in twenty-four hours and returned to normal twenty-four hours later.

These reports would seem to indicate that the degree of azotemia in the preceding cases was in direct proportion to the amount of blood in the gastrointestinal tract and to some extent depends upon how long the blood has been there.

Stevens and co-workers<sup>9</sup> in a recent paper agreed with the earlier work of Alsted<sup>4</sup> and showed much more conclusively that renal functions may be either normal or reduced in the presence of the azotemia which follows hematemesis. These authors studied 4 cases of hematemesis in which the blood urea nitrogen values were increased, the values ranging from 37 to 64 mg. per cent. The kidney function in these cases, as determined by the urea, inulin, and phenol red clearances and also by calculating the effective renal blood flow (from the phenol red clearance and hematocrit by using the average phenol red diodrast clearance ratio of 0.56 of Smith, Goldring, and Chasis<sup>10</sup>), was normal in one case and moderately decreased in the second case but considered not sufficiently reduced to account for the elevated blood urea nitrogen.

In the third case all of the clearances and the effective renal blood flow were reduced. However, fourteen days later no significant change in renal function or in effective renal blood flow was observed although the blood urea nitrogen was normal. The fourth case showed a reduction of all clearances and of effective renal blood flow. Three days later, when the blood urea nitrogen was 15 mg. per cent, there was no significant difference in either renal function or the effective renal blood flow. Stevens and associates<sup>9</sup> concluded from these observations that the reduction in the urea clearance may be due to the decreased renal blood flow but is insufficient to account for the increased blood urea nitrogen content and finally that the reduced clearance persists in spite of the return of blood urea to normal.

Recently Schiff and co-workers<sup>11</sup> gave citrated human blood by stomach tube to a group of 15 individuals free from renal disease. One thousand cubic centimeters were administered as a single dose to 7 members of the group, while a total dosage of 2,000 c.c. was given to the remaining 8 members in divided doses at four-hour intervals. A maximum blood urea nitrogen concentration of 24 to 57 mg. per cent was obtained within twenty-four hours of the single dose of blood. This was followed by a drop to normal on the second day in 5 and on the third day in 3 members of the group. The same typical rise within twenty-four hours and drop to normal also occurred in the remaining members receiving the total 2,000 c.c. of blood.

In discussing Schiff and associates<sup>11</sup> experiments, Crohn<sup>12</sup> stated that "the element of shock is the real factor, and the significant rises of urea occur only when the hemorrhage is acute, precipitate, and large in amount, and the rises of urea are proportionate to the degree of shock

rather than degree of loss of blood." This statement, in certain instances at least, does not apply to clinical cases and certainly is difficult to correlate with the experiments of Schiff and others and with ours that we will present in this paper.

Kaump and Parsons<sup>13-15</sup> also studied experimentally the azotemia following hemorrhage into the gastrointestinal tract. In his experiments varying amounts of blood were aspirated from the hearts of dogs. The blood was then given by stomach tube to the dogs. Blood urea determinations were made every four hours, following the ingestion of blood, for three days. Kaump observed a primary rise in blood urea in twenty-four hours followed by a drop to normal and a secondary lesser rise in forty-eight hours followed by a return to normal. He concluded that the azotemia produced was due (1) to the loss of blood and (2) to the increased absorption of blood from the gastrointestinal tract causing an increase in body protein.

#### EXPERIMENTAL

*Method.*—Citrated beef blood was given by stomach tube to a group of six dogs. The dogs were young, healthy females apparently free from renal disease. Their weights varied from 9 to 21.7 kg. and the hemoglobin values from 10.7 to 16.8 Gm. per 100 c.c.

Urea nitrogen determinations, using essentially the same method as that of Van Slyke and Cullen,<sup>16</sup> were made every four hours\* on blood from the external jugular vein of each dog from one to three days preceding each series of experiments. This was done in order to determine the normal blood urea nitrogen values for each dog since the individual animals were noted to show minor variations. Furthermore, it was found that each dog showed definite fluctuations in blood urea nitrogen values during the twenty-four hours. This was as much as 13 mg. per cent in some instances when the dogs were fed only once a day. As a rule the highest peak of the twenty-four hours' fluctuation was found to occur during the night. This was directly opposite to the findings of MacKay and MacKay<sup>17</sup> in normal human beings. However, the degree of fluctuation was comparable and could be decreased by divided meals. Therefore, during all experiments the dogs were given their usual amount of food divided into four small meals daily. Water was also given freely in the usual amounts.

After each blood urea nitrogen curve was established, the dogs were given varying amounts of citrated beef blood† by stomach tube in single and in divided doses. Three cubic centimeters of blood were taken from the jugular vein five times daily, as previously stated, for three to four days. Daily hematocrit and hemoglobin determinations were made.

\*Later changed to five specimens daily, taken at 12:00 M., 2:00 and 8:00 A.M., and at 4:00 and 8:00 P.M.

†Dog blood was used in two experiments as indicated in Fig. 1.

## RESULTS OF WHOLE BLOOD ADMINISTRATION

It was found that from three to seven hours after the administration of usually 200 c.c. of citrated beef blood by stomach tube, a definite elevation of blood urea nitrogen was present in twelve different experiments. Of the three dogs that received the single 200 c.c. dose of blood, a maximum blood urea nitrogen concentration was reached in from

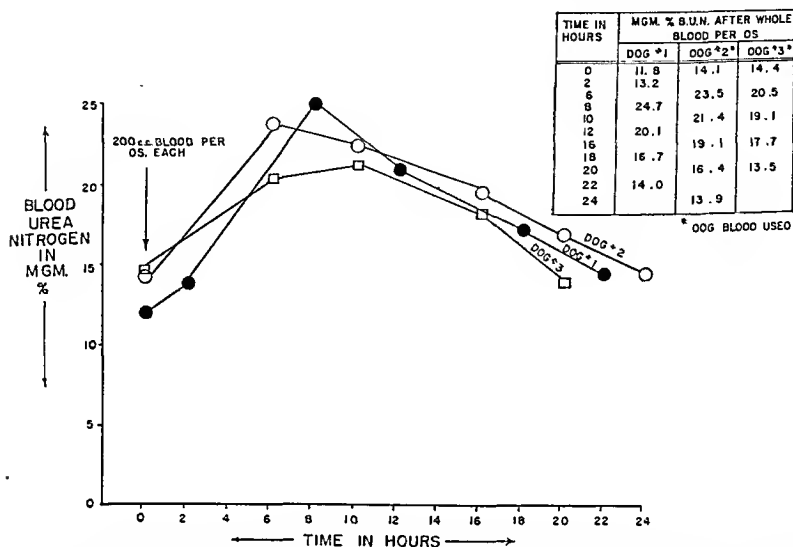


Fig. 1.—The effect of whole blood by stomach tube in the production of alimentary azotemia. Results are shown for three dogs after a single dose of blood. In each instance the curve extended for twenty-four hours before and after that shown with practically no rise.

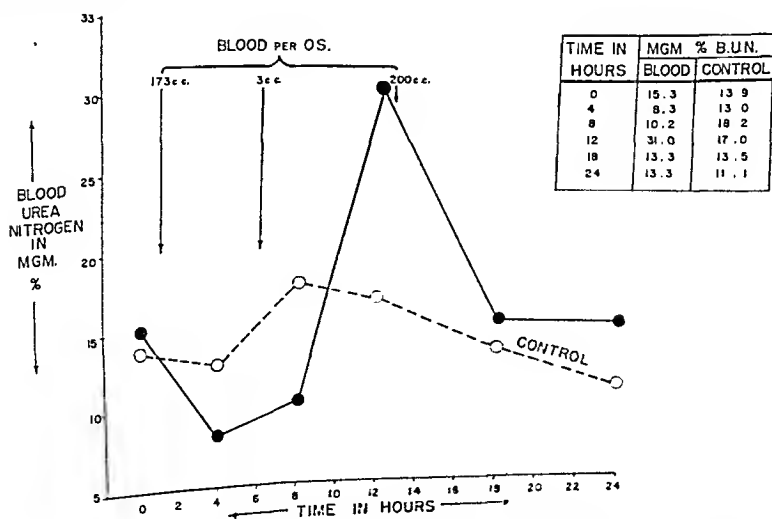


Fig. 2.—The effect of whole blood by stomach tube in the production of alimentary azotemia.

five and one-half to seven and one-half hours, and returned to normal levels in nineteen and one-half to twenty-one and one-half hours from the time the blood was administered as seen in Fig. 1.

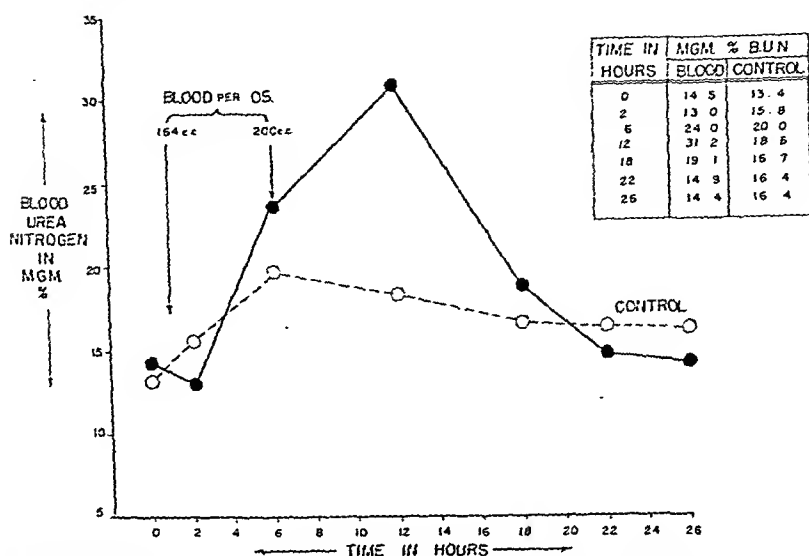


Fig. 3.—The effect of whole blood by stomach tube in the production of alimentary azotemia.

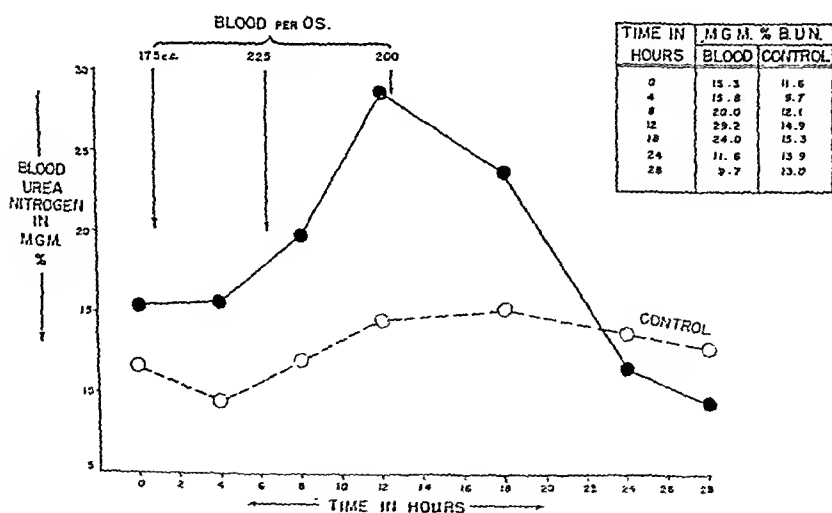


Fig. 4.—The effect of whole blood by stomach tube in the production of alimentary azotemia.

In the nine experiments in which the dogs received larger amounts of citrated blood in divided doses, the initial elevation of blood urea nitrogen was observed after intervals varying from three to eight hours. Two-thirds showed the elevation in five hours or before. The maximum

## RESULTS OF WHOLE BLOOD ADMINISTRATION

It was found that from three to seven hours after the administration of usually 200 c.c. of citrated beef blood by stomach tube, a definite elevation of blood urea nitrogen was present in twelve different experiments. Of the three dogs that received the single 200 c.c. dose of blood, a maximum blood urea nitrogen concentration was reached in from

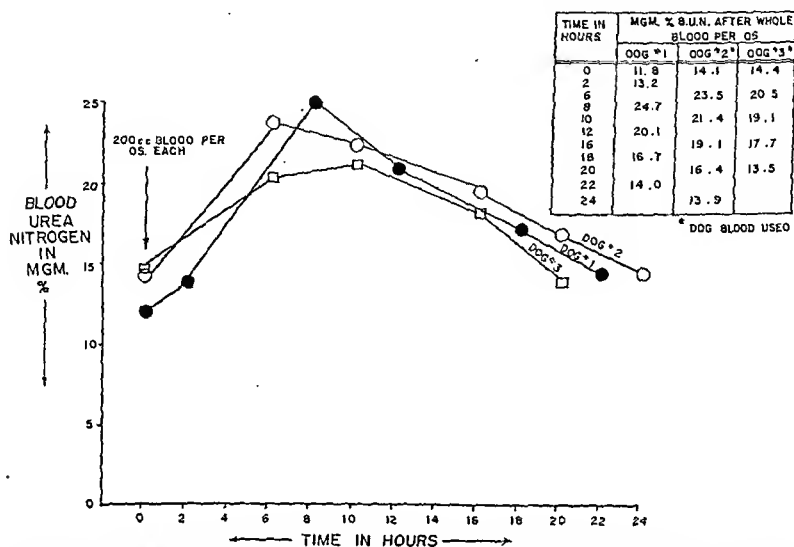


Fig. 1.—The effect of whole blood by stomach tube in the production of alimentary azotemia. Results are shown for three dogs after a single dose of blood. In each instance the curve extended for twenty-four hours before and after that shown with practically no rise.

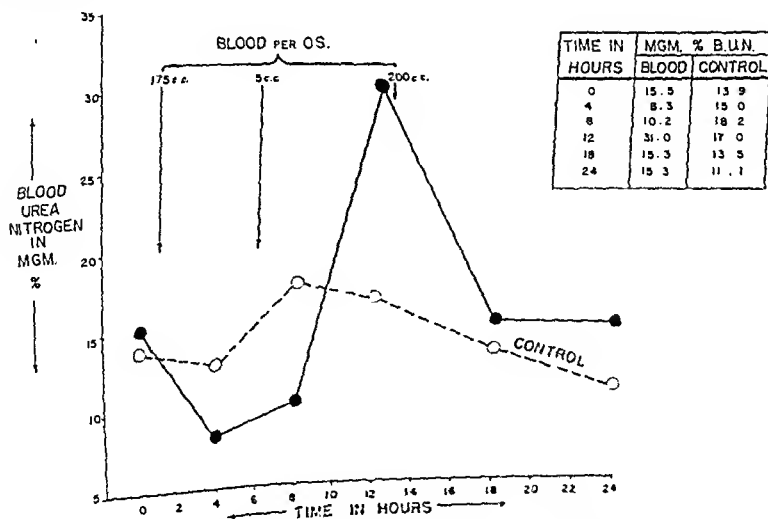


Fig. 2.—The effect of whole blood by stomach tube in the production of alimentary azotemia.

The daily hematocrit determinations revealed a slight but progressive anemia from day to day as the experiments proceeded. This, however, was so slight as to be of little importance either in the cause or prevention of azotemia as seen in Fig. 6. This figure indicates that, if anything, the dogs with slight anemia had a lower blood urea nitrogen value. This cannot be correlated with the fact that red cells contain more urea than plasma.

Blood urea nitrogen determinations were made on two cross-circulated dogs in terminal traumatic shock of over three hours' duration. These values were 21.9 and 22.9 mg. per cent, respectively. These are only slightly elevated above normal and represent what is in many cases only the upper limit of normal. During the period of shock the blood pressure of both dogs was below 60 mm. and showed a progressive fall; in addition there was a progressive hemoconcentration until death. Autopsy of both dogs revealed gross hemorrhagic congestion of the mucosa of the entire small bowel.

#### "ALIMENTARY AZOTEMIA," A PROPOSED NEW TERM

The name azotemia has been applied to this syndrome ever since Sanguinetti wrote his first description of it. The word azotemia is derived from two Greek words meaning "life blood" and prefixed by "a" to give the meaning "negative life blood." The term azotemia later came to mean the presence of urea or other nitrogenous bodies in the blood, especially when in increased amounts.

Reasoning from analogy to the commonly used term alimentary glycosuria (which might be more properly termed alimentary hyperglycemia), it seemed logical to us that the urea syndrome be termed alimentary azotemia. The mechanism in each case is the same and the adjective is used in both instances to differentiate the condition under consideration from a similar one in result but a different one in causation. Use of the name extrarenal azotemia is not definitive enough and furthermore leads to confusion with the so-called hepatorenal syndrome which we believe is not at all related to the condition we are considering.

#### SUMMARY

A review of the literature was made concerning the etiology of azotemia following hemorrhage into the gastrointestinal tract.

The intragastric administration of citrated beef blood in twelve experiments on six dogs revealed an initial elevation of blood urea nitrogen in three to eight hours, a maximum concentration in five and one-half to nineteen hours (depending on amount given and number of doses), and a return to normal levels in six to nineteen and one-half hours following the last administration of blood. The dogs were not starved, dehydrated, markedly anemic, hypochloremic, or in shock. Admin-

blood urea nitrogen concentration was obtained in anywhere from five and one-half to nineteen hours, depending on the amount of blood and the number of doses. The return to normal after the maximum blood urea nitrogen concentration was reached occurred quite rapidly in most cases, as seen in Figs. 2, 3, and 4. However, the average total length of time during which azotemia exists was increased when very many blood administrations were given, as seen in Fig. 5.

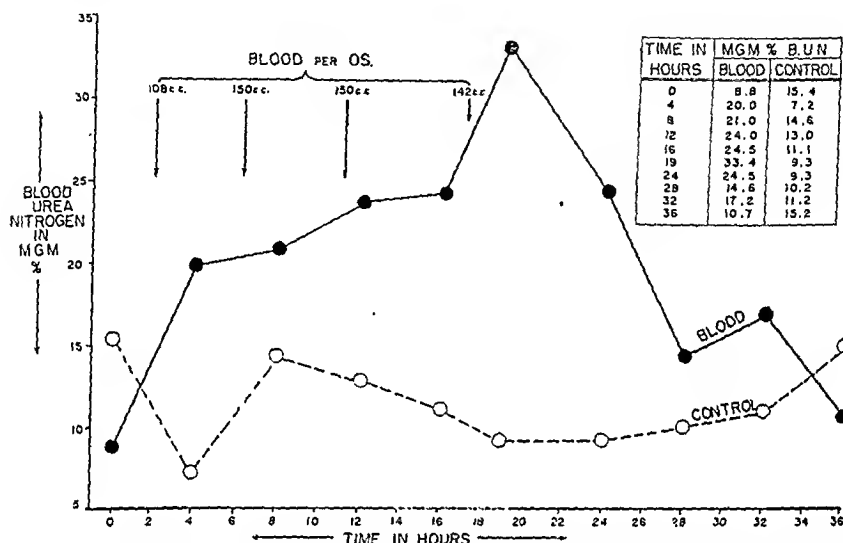


Fig. 5.—Staircase effect of repeated doses of blood by stomach tube in the production of alimentary azotemia.

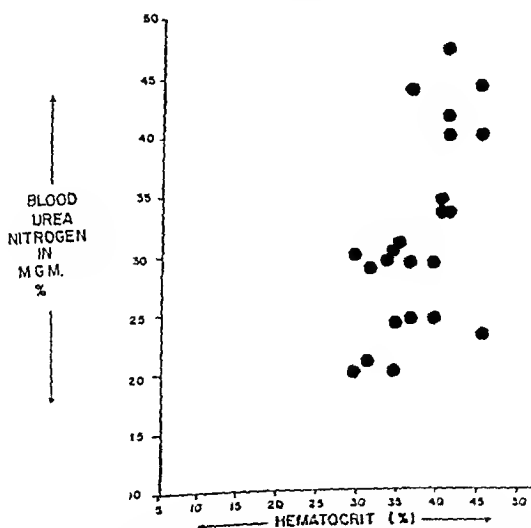


Fig. 6.—Lack of correlation between anemia and blood urea nitrogen elevation. Highest values of blood urea nitrogen in twenty-three experiments and coexistent hematocrit percentages. It is to be noted that, if anything, a line drawn through the average of the charted points would slant from left below to right above indicating actually decrease in the blood urea nitrogen level with low hematocrit.

11. Schiff, L., Stevens, R. J., Goodman, S., Garber, E., and Lublin, A.: Observations on the Oral Administration of Citrated Blood in Man. I. The Effects on the Blood Urea Nitrogen, *Am. J. Digest. Dis.* 6: 597-602, 1939.
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istered blood was carefully analyzed and found normal in blood urea nitrogen content as shown in Table I.

TABLE I  
ANALYSIS OF SPECIMENS OF WHOLE BEEF BLOOD USED FOR INTRAGASTRIC  
ADMINISTRATION TO DOGS IN THESE EXPERIMENTS

SPECIMEN NO.	HEMOGLOBIN GM. %	HEMATOCRIT %	UREA NITROGEN MG. %	TOTAL PLASMA PROTEIN GM. %
1	11.0	33.0	19.1	4.30
2	12.6	35.0	9.9	4.96
3	13.0	37.0	17.7	5.20
4	10.0	35.5	16.1	4.52
5			16.9	
Average	11.7	35.1	15.9	4.74

Blood urea nitrogen values were only slightly elevated in two dogs in terminal traumatic shock.

#### CONCLUSIONS

1. An increase in blood urea nitrogen occurs in the dog following the intragastric administration of whole blood.

2. In these experiments starvation, dehydration, bleeding, hypochloremia, and shock did not play a major part in the production of azotemia.

3. The term alimentary azotemia is proposed for this condition and it seems logical to assume that much of the rise in blood urea nitrogen observed in clinical cases of bleeding peptic ulcer is due to the same phenomenon.

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studied in dogs. Three methods were employed: (1) intravenous injection of commercial trypsin solution containing large amounts of amylase and lipase, besides the trypsin; (2) infusion of blood from a dog with acute pancreatic damage into a normal animal; and (3) injections of acetyl-betamethylcholine and eserine.

Serum amylase was determined using the one-half-hour method of Wohlgemuth.<sup>10</sup> Amylase concentration is expressed by the degree of dilution at which 1 c.c. of the diluted serum will still hydrolyze 1 c.c. of an 0.1 per cent starch solution at 38° C. within thirty minutes. We are aware of the shortcomings of this method. We chose it, however, because we were interested in considerable changes of the serum amylase rather than in small variations. Besides, the method is reliable and is particularly fit for clinical purposes. Serum lipase was estimated by the method of Crandall and Cherry;<sup>5</sup> units of lipase are expressed in cubic centimeters of n/20 NaOH.

## EXPERIMENTS

1. Each of two dogs weighing 15 and 18 kg. received an intravenous injection of 20 c.c. of a filtered 2 per cent solution of commercial trypsin 1:200\* in saline solution. Table I shows the amylase and lipase values found in the trypsin solution and in blood samples drawn from the dogs

TABLE I

SERUM AMYLASE AND LIPASE FOLLOWING INTRAVENOUS INJECTION OF 20 C.C. OF 2 PER CENT TRYPSIN SOLUTION

	AMYLASE	LIPASE
<i>Experiment 1</i>		
Trypsin solution	64,000	4.70
Dog's serum		
Before injection	128	0.60
After injection		
5 min.	512	2.20
30 min.	512	
1 hr.	512	
2 hr.	512	3.60
3 hr.	256	3.80
4 hr.	256	3.60
5 hr.	256	3.40
7 hr.	256	
9 hr.	128	0.60
<i>Experiment 2</i>		
Trypsin solution	64,000	9.84
Dog's serum		
Before injection	128	0.00
After injection		
10 min.	512	1.64
1 hr.	256	3.32
2 hr.	256	2.24
4 hr.	256	
6 hr.	128	1.48
8 hr.	128	1.20
24 hr.	128	0.60

\*We are obliged to Dr. D. Klein, Wilson Laboratories, Chicago, for a supply of concentrated trypsin.

STUDIES ON PANCREATITIS\*  
OBSERVATIONS ON THE DISAPPEARANCE OF EXPERIMENTALLY INCREASED  
BLOOD AMYLASE AND LIPASE  
H. L. POPPER, M.D., AND F. PLOTKE, M.D., CHICAGO, ILL.  
(From the Department of Gastro-Intestinal Research of Michael Reese Hospital)

THE RECENT interest in acute pancreatic disease has brought forth a great number of publications on blood amylase and lipase. In earlier papers the senior author (H. L. P.) stressed the clinical importance of the blood amylase test and its diagnostic limitations;<sup>1, 2</sup> it was found that, while the concentration of lipase<sup>3</sup> may be of diagnostic value, the results often are not as constant and unequivocal as those of amylase tests. These lipase tests were performed by determining the concentration of atoxyl-resistant tributyrin-splitting enzyme. Chiray, Berdet, and Taschner<sup>4</sup> and Crandall and Cherry<sup>5</sup> have shown that an olive oil-splitting enzyme, i.e., a true lipase, and not a tributyrin-splitting esterase is increased in concentration in the blood more or less regularly in experimental and clinical disturbances of the pancreas. Clinical investigations of this lipase have not been performed on a larger scale, except by Comfort and Osterberg.<sup>6</sup> Their results are, however, very similar to those obtained by the senior author (H. L. P.) on atoxyl-resistant esterase.

Daily determinations in acute pancreatic disease have shown that the increase of blood amylase concentration is present only for a limited time. The concentration begins to decline after a few days and a normal level is re-established very soon, whether the pathologic process in the pancreas is progressive or not. This fact reduces greatly the diagnostic value of the amylase test; normal amylase values would preclude acute pancreatic disease only if performed within three to five days of the suspected attack. Blood enzyme studies in cases of disturbance of the pancreas following gall bladder surgery<sup>7</sup> and stomach resection<sup>8</sup> have shown us that sometimes the amylase concentration of the blood decreases even before the third day, indicating that the pathologic process in the pancreas was receding. It is an open question as to why the elevation of blood amylase and lipase in acute progressive pancreatitis is of such short duration. It would seem logical to assume, for the time being, that this elevation persists only for such a period of time as the glands of the pancreas remain functioning and thus enzymes may be liberated into the blood and lymph.<sup>9</sup>

In order to put this assumption to an experimental test, the rate of disappearance of artificially raised blood enzyme concentration was

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gradually in the subsequent blood samples and after five hours amylase concentration had returned to its original level. The lipase concentration of the infused blood was increased but slightly and no appreciable change of the serum lipase level was found in the second dog.

3. Finally the duration of increased concentration of blood enzymes following drugs which stimulate secretion of the pancreas was determined (Table III).

Recently Antopol, Schiffrin and Tuchman<sup>12</sup> as well as Friedman and Thompson<sup>13</sup> have shown that injection of acetyl-beta-methylcholine and eserine causes an increase of the blood amylase concentration in dogs and they demonstrated that this was due to stimulation of the pancreas.

A dog of 11 kg. body weight received 3 mg. of acetyl-beta-methylcholine (mecholy1)\* and 0.5 mg. of eserine sulfate by hypodermic injection. The highest level of serum amylase was found (Table III), 3½ hours

TABLE III  
SERUM AMYLASE AND LIPASE FOLLOWING SUBCUTANEOUS INJECTION OF  
MECHOLYL AND ESERINE

EXPERIMENT 4	AMYLASE	LIPASE
Before injection	128	0.40
After injection		
1 hr.	256	1.70
3½ hr.	1024	1.70
6 hr.	512	0.30
8½ hr.	512	0.20
11 hr.	256	0.20
24 hr.	128	0.00

following administration of the drugs. Then the amylase concentration decreased slowly and returned to its original level between the eleventh and twenty-fourth hours. Determinations of serum lipase showed a distinct but not very marked increase after 1 hour; after 3½ hours the concentration was still unchanged, but after 6 hours the original lipase level had been re-established.

#### RESULTS

Serum amylase rose to a fourfold concentration in Experiments 1, 2, and 3. Return to the original level took place between the seventh and ninth hours in Experiment 1, between the fourth and sixth hours in Experiment 2, and between the third and fifth hours in Experiment 3. Experiment 4 showed an eightfold increase of serum amylase 3½ hours after injection of the drugs, and a return to its original level took place between the eleventh and twenty-fourth hours after injection. Inasmuch as it had decreased considerably 11 hours after administration of the drugs, we may assume that the original level had been attained shortly afterwards.

Experiments 1, 2, and 3 show that the body begins to eliminate an increased blood amylase very promptly. The longest persistence of

\*We are obliged to Merck & Co., Inc., Rahway, N. J., for supplies of mecholy1.

before and at regular intervals after its administration. A marked increase of both serum amylase and lipase was found a few minutes after injection. In Experiment 1 serum amylase remained at this elevated level for some time and began to decline after 2 hours; whereas, a decline was found in Experiment 2 after 1 hour. The original level of amylase was re-established in Experiment 1 after 9 hours; in Experiment 2, after 6 hours. Serum lipase showed a progressive increase. The highest value appeared in Experiment 1 after 3 hours; in Experiment 2, after 1 hour. The restoration of the original lipase level was found in Experiment 1 after 9 hours; in Experiment 2 a slight increase of lipase was still present after 8 hours; 24 hours after injection the serum lipase had returned to a normal level.

The injection of the trypsin solution was followed by marked symptoms of shock. We believe that our results are nevertheless instructive because acute pancreatic disease in man is very often accompanied by shock and because shock will probably retard and not shorten the return to normal of blood enzyme concentration.

These experiments, however, were performed with administration of heterologous enzymes and the results are open to objection. Therefore, the following experiments were performed.

2. Two dogs with compatible blood were used.<sup>11</sup> Acute damage of the pancreas was produced in one of them under nembutal anesthesia by injection of 3 c.c. of its own gall bladder bile into the main pancreatic duct and subsequent ligation of the duct. Serum amylase of this dog was determined every hour and after six hours a marked increase of blood amylase was found. At this time citrated blood was withdrawn aseptically and stored in a refrigerator. On the following day blood was drawn from the second dog and replaced immediately by the warmed blood from the first dog. This procedure was repeated several times until approximately 60 per cent of the circulating blood had been replaced. Serum amylase and lipase concentration of the stored blood and of blood samples drawn from the infused dog before and at regular intervals after the blood exchange are shown in Table II.

TABLE II  
INFUSION OF PANCREATITIS BLOOD INTO DOG

EXPERIMENT 3	AMYLASE	LIPASE
Pancreatitis blood serum	512	1.00
Dog's serum	64	0.00
Before infusion	256	0.00
After infusion	128-256	0.20
1/2 hr.	128	0.00
1 hr.	64	
3 hr.		
5 hr.		

The highest concentration of amylase was found in the first sample, drawn one-half hour after infusion. The amylase level declined

2. The secretory function of the damaged pancreas stops usually three to five days after the beginning of the disease, and this is followed by a decrease of the blood amylase level. If the blood amylase level declines before that time, one may conclude that a less severe pathologic process of the pancreas is subsiding.

We are obliged to Dr. H. Necheles, Dr. F. Neuwelt, and Mr. Wm. Olson for advice and help.

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increased amylase was found in Experiment 1 in which it remained at the same high level for 2 hours. But in Experiments 2 and 3 the beginning of decline was demonstrable already within the first hour. Experiment 4 must be considered separately because the effects of the drugs seem to persist for some time, apparently causing a prolonged discharge of enzymes into the circulation. The fact that in this experiment the serum amylase level rose to its maximum value during the first  $3\frac{1}{2}$  hours after injection shows that at first the amount of enzyme which entered the circulation did exceed the amount eliminated. After  $3\frac{1}{2}$  hours, however, a gradual decrease occurred.

It is very probable that there is an analogous course of the blood enzyme curve in human pancreatitis. One may assume that persistence of high blood amylase in acute pancreatic disease is caused by a continuous entrance of more enzymes into the circulation than can be eliminated, and that during this period the pathologic process in the pancreas is active.

A diminishing or a decreased level of serum amylase, on the other hand, shows that the discharge of enzyme into the circulation is lessening and that, therefore, the balance of inflow and elimination has become negative. Damage to the pancreas is accompanied by an inflow of amylase into the circulation for a few days (usually three to five days), and after this time the secretory activity of the pancreas has probably ceased by damage or by destruction of the organ. Thus, a decrease of blood amylase usually occurs three to five days after the beginning of pancreatitis in man, in spite of the continuation of the pathologic process. On the other hand, an earlier decline of blood amylase concentration indicates the subsiding of pancreatic disease, usually of lesser severity.

Blood lipase levels behaved similar to those of amylase in Experiments 1, 2, and 4. Restoration of normal lipase concentration occurred within several hours. It is of interest to note that mechoyl and eserine raise both the amylase and the lipase concentration of the blood.

#### SUMMARY AND CONCLUSIONS

The time for elimination of increased blood amylase and lipase was studied in dogs after intravenous administration of commercial trypsin solution (containing also lipase and amylase), after transfusion of blood rich in amylase, and after injection of mechoyl and eserine. Elimination of increased blood amylase and lipase begins very quickly and lasts several hours. It is believed that the level of blood amylase and lipase is determined by the balance between their inflow into, and their elimination from, the circulation.

The results of our experiments permit the following conclusions on the concentration of blood enzymes in human pancreatitis:

1. A high blood amylase level over several days indicates that enzyme inflow into the circulation exceeds the elimination and is a sign of an active pathologic process in the pancreas.

closure of the duodenum and reimplantation of the pancreatic and bile ducts into the duodenum at the site of the anastomosis. Although the method has since been employed many times, the results have been unsatisfactory.

Cooper<sup>3</sup> in December, 1937, reported 14 cases of carcinoma of the ampulla of Vater with no cures.

Hope of cure in the larger and more infiltrative lesions lies only in radical resection, preferably in stages. These patients are jaundiced and are poor operative risks. The initial procedure, following adequate preoperative preparation, should be to relieve the jaundice. A preliminary cholecystotomy may be performed, if necessary. If the patient's condition will permit, it is believed best to open the abdomen, establish the diagnosis, and construct a cholecystojejunostomy on the Roux principle. The second stage may be performed after a few weeks when the jaundice has cleared, the bleeding time has returned to normal, and the patient is in condition to withstand the radical resection.

The anastomosis of the gall bladder to the jejunum, on the Roux principle, was carried out on the following case. This was recommended by Whipple<sup>2</sup> in 1938, but there has been no other case reported in which a two-stage resection has been completed in this manner.\*

#### CASE REPORT

The patient, E. T. E., a white male, 38 years of age, was admitted April 18, 1939. Jaundice first appeared in August, 1938, associated with attacks of colicky pain in the right upper quadrant. Stools became clay colored, jaundice increased, and weakness and weight loss were progressive. Bright red blood was found in the stools in January, 1939, at which time the patient was bedridden and had noted a total weight loss of forty pounds. In February, 1939, a cholecystotomy was performed elsewhere. There was a temporary decrease in the jaundice, but drainage was inadequate due to the formation of several fistulas and pocketing of bile in the abdominal wall, and in a few weeks the jaundice became as deep as before the operation.

Examination revealed an undernourished white male with deep clinical jaundice. There was a right rectus scar healed except for a biliary fistula. Another fistula to the right was located over a swelling of the abdominal wall from which about 90 c.c. of bile could be expressed. The liver was 10 cm. below the costal border. There was no intra-abdominal fluid. Temperature was 98.4°; respiration, 14; pulse, 66; blood pressure, 110/72.

The laboratory findings were as follows: Urinalysis: 2 plus albumin, moderate W.B.C., occasional R.B.C., bile present. Blood examination: Erythrocytes, 4.4 million; hemoglobin, 80 per cent; leucocytes, 5,000. Coagulation time was five minutes and bleeding time was two minutes. Serology was negative. The icterus index was reported 16.5, although the patient appeared to be deeply jaundiced. The van den Bergh test gave a delayed direct reaction. An x-ray of the chest was normal. Lipiodol injected into the biliary sinus showed a collection in the abdominal wall and did not visualize the biliary tract.

\*Although Whipple has completed Roux procedures in two cases, the patients did not survive sufficiently long for him to consider them of any value as data in reporting the procedure (personal communication).

## TWO-STAGE RESECTION OF CARCINOMA OF THE AMPULLA OF VATER\*

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THE RADICAL two-stage resection of carcinoma of the ampulla of Vater was first advocated by Whipple, Parsons, and Mullins<sup>1</sup> in 1935. In April, 1938, Whipple<sup>2</sup> collected and briefly reported 11 cases in which radical resections had been performed. Although the two-stage procedure was not employed in all, patients in 5 of these 11 reported cases survived the operation. Brunschwig<sup>3</sup> in November, 1937, reported a successful two-stage resection of the duodenum and head of the pancreas for carcinoma. The patient died on the eighty-fifth postoperative day of extensive intra-abdominal metastases. Crile<sup>4</sup> in October, 1938, reported a successful resection of the head of the pancreas by the two-stage method but the patient died eighteen months later.† Illingworth<sup>5</sup> in May, 1939, reported a case in which a two-stage resection was performed. The patient died on the forty-third postoperative day due to leakage from the stump of the common bile duct.

Until recently radical operations on the pancreas were seldom considered justified and resections were attempted almost exclusively for small growths about the ampulla. These tumors were approached either through the anterior wall of the duodenum or from behind after mobilizing the duodenum. The bile and pancreatic ducts were severed and usually left to drain into the crater in the head of the pancreas and through the opening into the duodenum. The results obtained by these surgical procedures were not good; operative mortality was very high and pancreatic and biliary fistulas were frequent. Postoperative complications and recurrences were common. Of the 76 cases reported by Hunt and Budd<sup>6</sup> in 1935, there were 29 deaths, a mortality of 39 per cent. Because of the short follow-up, the end results are difficult to evaluate, but there probably were only 7 cures out of the 76 cases (9 per cent).‡

Halsted<sup>7</sup> in 1893 removed a full segment of the duodenum and a wedge-shaped section of the head of the pancreas with end-to-end

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†The patient died as a result of a stricture of the cholecystogastrostomy anastomosis. Shortly before death he developed typical vitamin A deficiency with night blindness and keratoses (personal communication).

‡This high percentage of cures may be attributed to several factors, the most important being the size of the tumor resected which varied from a "pea" to "robin's egg size."

*First Operation.*—Following preparation with high carbohydrate diet, intravenous solutions of glucose and calcium gluconate, and administration of vitamins, including vitamin K and bile salts, the patient was operated upon May 15, 1939.

Under general anesthesia a right rectus incision was made and the biliary sinuses of the abdominal wall were excised. Many intra-abdominal adhesions were separated. The liver was enlarged about 10 cm. below the costal margin. The gall bladder was distended and the wall thickened. The common bile duct was dilated to 2.5 cm. in diameter. In the head of the pancreas a stony hard nodular mass was palpated, approximately 5 cm. in diameter. No metastases nor enlarged lymph nodes were found. A diagnosis was made of carcinoma of the head of the pancreas and ampullary region. Approximately 20 inches below the ligament of Treitz, the jejunum was severed between clamps. An antecolic anastomosis was established between the gall bladder and the distal jejunum, and an end-to-side anastomosis was established between the proximal jejunum and the distal jejunum at a site approximately 10 inches below the cholecystojejunostomy. (Fig. 1.) The mesentery was closed to prevent hernia. Care was taken to avoid constricting the transverse colon. The postoperative recovery was uneventful with disappearance of the jaundice and rapid gain in weight and strength. Fine catgut technique was used throughout.

*Second Operation.*—On July 10, 1939, under spinal anesthesia later supplemented with general anesthesia, a wide transverse incision was made. Many adhesions were incised. The previously constructed anastomoses were examined and an adequate stoma found in each. The tumor was palpated, found to be about the same size, and was again considered operable. The duodenum was mobilized by dividing its right lateral peritoneal attachment, permitting the growth to come forward with it. The common bile duct, the superior mesenteric vein, and the portal vein were then exposed and were found to be free from the tumor. The common bile duct was doubly ligated and severed below the cystic duct. The pancreatoduodenal artery was ligated. The duodenum was then divided near the pylorus and again in its third portion, and the ends closed. The pancreatic duct was exposed and a wedge-shaped section of the pancreas was removed, the dissection extending along the wall of the superior mesenteric and portal veins. (Fig. 2.) Care was taken to avoid cutting close to tumor tissue. The dilated pancreatic duct was isolated and suture ligated. A small rent made in the portal vein was sutured. Bleeding from the large duodenal and pancreatic branches of the superior mesenteric vessels was controlled temporarily by packing and later by ligation. The raw pancreatic surface could not be closed completely although several interrupted mattress silk sutures were placed to bring it together partially and to reduce the drainage of pancreatic juice. Because of a very short transverse mesocolon, an anterior gastrojejunostomy was performed. Drains were placed down to the area of pancreas resected and the abdomen was closed. (Fig. 3.) During the operation 1,500 c.c. of blood and 5,000 c.c. of 5 per cent glucose solution were administered. The blood pressure remained fairly constant at about 110/65. The pulse varied from 84 to 110. During a period of considerable bleeding, the pulse became much weaker and slightly irregular, but with the administration of blood and fluids it quickly improved. On completion of the six-hour operation, the respiration was 20, pulse was 96, blood pressure was 110/64.

*Postoperative Course.*—During the evening of the operation the temperature reached 105° and the pulse 126 for a few hours. The next day the temperature was 102.6° and four days later was normal. From the fourth to the tenth post-operative day there was considerable bile drainage from the wound, after which drainage stopped and the wound healed without hernia. The patient was up in fourteen days. About one month later he complained of cramping pain in the right upper abdomen. There was no distention, no fever, and, after receiving a "sterile hypo," he was asleep in ten minutes. Two months later, he had a chill

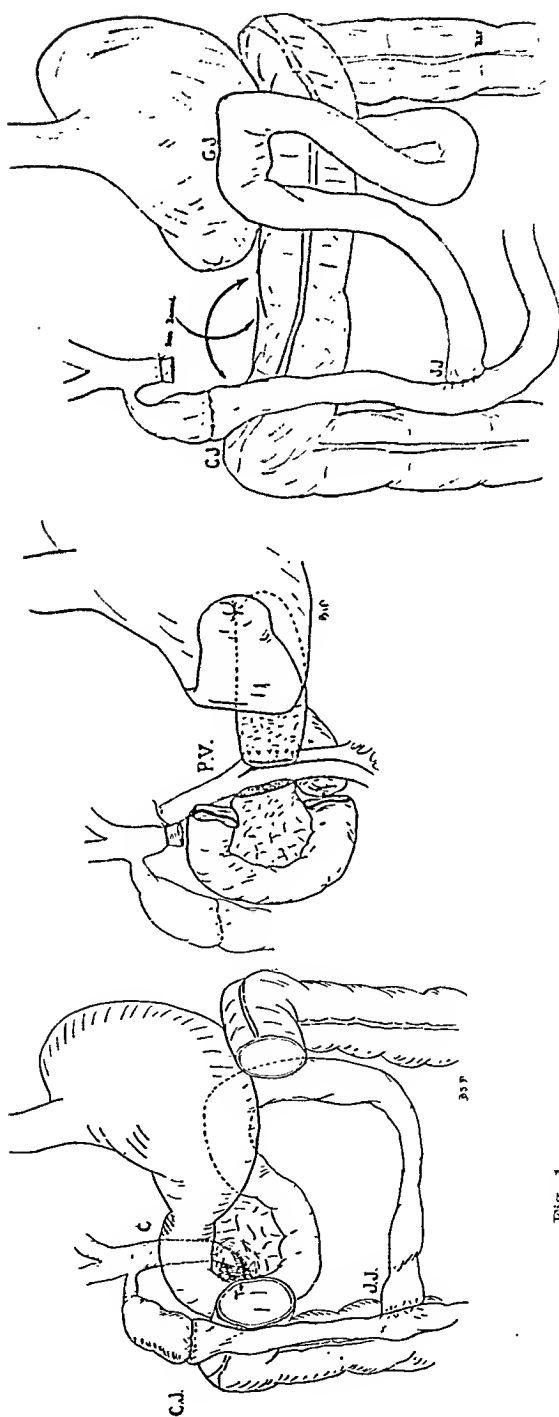


Fig. 1.

Fig. 2.

Fig. 3.

Figs. 1-3.—Technique of operation. Fig. 1, Completion of first stage of operation, showing tumor (*T*) blocking the common bile duct (*C*) and completed cholecystojejunostomy (*CJ*) and jejunojejunostomy (*JJ*). Fig. 2, Second stage, showing line of incision of pancreas along the portal vein (*PV*), ligation of dilated common bile duct, and transection of the duodenum. Fig. 3, Completion of second stage with anterior gastrojejunostomy (*GJ*); arrows show area drained.

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followed by a temperature of 102°. The next day the temperature was normal and remained so during this period of hospitalization. The blood sugar after operation was 101 mg. Stools revealed the usual normal amount of undigested fat as compared with two controls, all on a regular diet. The patient looked and felt a well man when discharged Sept. 21, 1939, having regained twenty of the forty pounds lost.

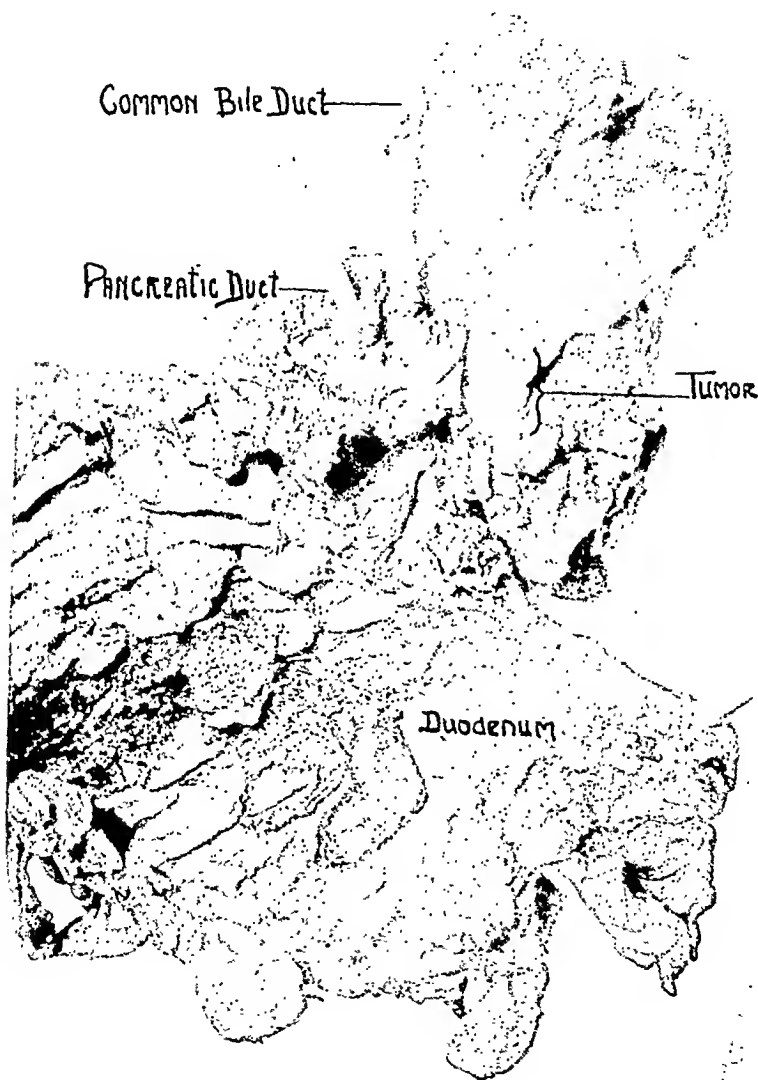


Fig. 4.—Operative specimen of duodenum, head of pancreas, lower end of common bile duct and tumor.

*Pathologic Report.*—The specimen consisted of a 20 cm. section of duodenum, the distal 5 cm. of the common bile duct, and the head of the pancreas with its duct. The mucosa of the duodenum was intact. The papilla of Vater was enlarged and felt firm on palpation. The common bile duct was considerably dilated. The

lumen of the terminal portion of the duct was markedly constricted and did not permit the passage of a probe. At the site of constriction the duct had an annular superficial ulceration measuring 1 cm. in length. The underlying wall was markedly thickened, was indurated, and was composed of a grayish white tissue which infiltrated to a slight extent the underlying pancreatic tissue and the posterior portions of the ampullary part of the duodenum. The pancreatic duct was slightly dilated. It opened directly into the duodenum at the papilla of Vater. There was apparently compression of the termination of the duct by the mass at the termination of the common bile duct. The pancreatic tissue appeared to be normal.

*Microscopic Report.*—Section through the tumor mass revealed marked thickening of the wall of the common bile duct and the outer coats of the duodenum with infiltration of many masses and columns of large epithelial cells. The cells were large and irregular and had large hyperchromatic nuclei which varied in size. In a few areas the epithelial cells formed small acini. One section of the pancreas showed invasion of the capsule and fibrous trabeculi by tumor cells. The pancreatic acini, ducts, and islands of Langerhans appeared normal. *Summary:* Adenocarcinoma of the ampullary region of the duodenum, probably arising in the terminal end of the common bile duct and invading the head of the pancreas.

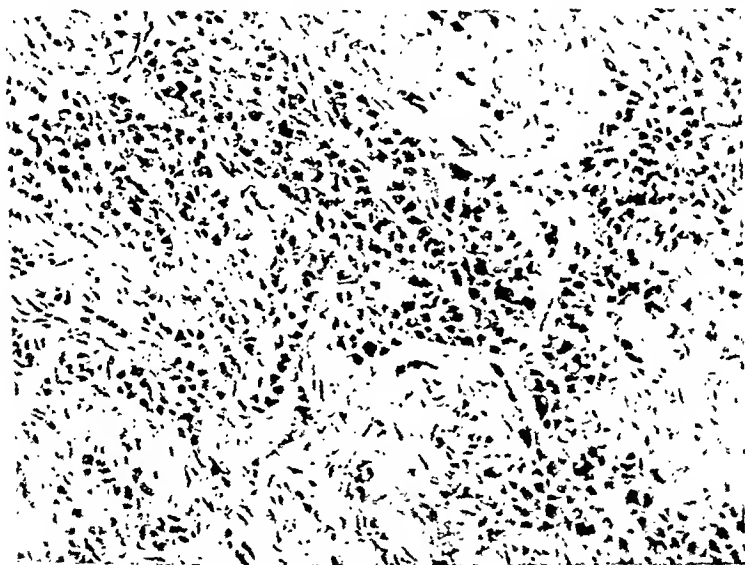


Fig. 5.—Photomicrograph of tumor of ampullary region. Anaplastic adenocarcinoma.

*Readmission.*—The patient was rehospitalized Nov. 12, 1939, four months after the last operation, seriously ill, complaining of jaundice, evident loss of weight, ascites and edema of the lower extremities. The liver was enlarged down to the umbilicus and was questionably nodular and definitely tender. Stools were acholic when he was admitted, but within a few days became green and contained much bile. Urine contained bile. Laboratory examinations gave the following results: Blood count: erythrocytes, 3.1 million; hemoglobin, 65 per cent; leucocytes, 11,600; polymorphonuclears, 50 per cent; lymphocytes, 14 per cent; monocytes, 6 per cent. Blood chemistry revealed a blood sugar of 80 mg. per 100 c.c.; urea nitrogen, 14.1 mg. per 100 c.c.; cholesterol, 191 and 241 mg. per 100 c.c.; prothrombin time, 66 per cent normal; blood proteins, 5.91; blood globulin, 2.7. The stools contained undigested fat. Many of these examinations were repeated with but little sig-

nificant change. Abdominal paracentesis was performed several times and large quantities of clear amber fluid were removed. Therapeutic measures included blood transfusion, antianemic and high carbohydrate diet, administration of hemopoietic preparations and vitamins, including vitamin K, intravenous glucose solutions, and administration of raw, ground pancreas, 100 Gm. three times a day. This was later changed to the extract of pancreas, lipocnie, three capsules three times a day (obtained through the courtesy of Dr. L. G. Dragstedt and the Eli Lilly Co.). In spite of these measures the patient pursued a progressively downhill course and expired Dec. 9, 1939, five months after the last operation.

*Autopsy.*—There was scar tissue at the site of resection of the duodenum and head of the pancreas with no local recurrence of the carcinoma. A regional lymph node, several centimeters distant, about 1.5 cm. in size, on microscopic examination showed partial replacement by carcinoma cells. The pancreas appeared normal both grossly and microscopically. There was no dilatation of the ducts. The liver contained discrete areas of metastatic carcinoma replacing approximately 20 per cent of its substance. There was also a severe suppurative cholangitis and hepatitis. Microscopically the liver cells showed retained bile pigment, albuminous degeneration of cytoplasm, and infiltration with many lymphocytes and a few polymorphonuclear leucocytes. These changes were believed to be due to infection. There was no fatty degeneration or atrophy as has been described in experimental animals following ligation of the pancreatic ducts.

#### COMMENT

Crile stated that in eight autopsies at the Cleveland Clinic for carcinoma of the head of the pancreas, six were resectable. In 60 per cent of the surgical cases of Rives, Romano, and Sandifer<sup>9</sup> no metastases were found at operation. Ransom's<sup>10</sup> autopsy figures indicate that primary carcinoma of the bile ducts and of the ampulla of Vater is actually more common than primary carcinoma of the head of the pancreas and that many of these tumors are localized and resectable even at the time of the patient's death.

Metastases from carcinoma of the ampulla of Vater are relatively infrequent, partly because these tumors produce symptoms early and partly because these tumors are usually not highly malignant. Tumors arising in the head of the pancreas produce symptoms later, are more malignant, and metastasize earlier, hence the importance of making the differentiation whenever possible. In the early case differentiation is often not possible and resection is indicated. A large percentage of the tumors of the ampullary region and head of the pancreas actually arise in the ampulla of Vater, are of low-grade malignancy, and produce symptoms early. Every patient with persistent painless jaundice of the obstructive type should have the benefit of an exploratory operation with resection of the tumor if one is found and is operable. The feasibility of surgery in these cases has greatly increased due to our recent knowledge and use of vitamin K.

#### SUMMARY

1. A carcinoma of the ampulla of Vater with infiltration into the head of the pancreas was successfully resected by a two-stage procedure.

This is believed to be the first case reported in which resection has been completed with a Roux cholecystojejunostomy, as advocated by Whipple. Although a formidable procedure, the principle is sound, permitting wide removal of all cancer tissue.

2. Death occurred five months later. Autopsy revealed a small metastasis in a regional lymph node, metastases in the liver, suppurative cholangitis, and hepatitis. There was no local recurrence of the carcinoma.

3. Recent advances in the surgery of jaundiced patients should encourage resection in selected cases with lower operative mortality.

4. Two serious complications may occur following this type of resection: (1) fatty degeneration and atrophy of the liver, probably preventable by the administration of raw pancreas or certain pancreatic extracts; (2) cholangitis, which is believed to be a frequent complication after all types of gall bladder anastomoses. The Roux anastomosis is simply constructed and functions well postoperatively. Whether or not the incidence of cholangitis is higher following this anastomosis than following anastomosis of the gall bladder to the stomach has not been definitely determined.

5. A high percentage of tumors of this region are of low-grade malignancy. This tumor, however, on microscopic examination was found to be anaplastic and highly malignant. This was substantiated by the subsequent development of liver metastases.

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# SURGICAL MASKS

## AN EXPERIMENTAL STUDY

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IN THE latter part of the nineteenth century Flügge and his associates<sup>10, 11, 12, 21</sup> demonstrated that bacteria are expelled from the nose and mouth during the acts of talking, coughing, and sneezing. Among the early workers Hamilton<sup>13</sup> in 1905 showed that scarlet fever patients spread hemolytic streptococci by means of their invisible sputum, and a few years later Teague<sup>27</sup> reported that diphtheria bacilli were emitted by more than one-half of his diphtheria patients when they coughed or talked. The importance of these observations has been forcefully pointed out to surgeons by Meleney and Stevens<sup>20</sup> and Paine,<sup>33</sup> who proved that strains of hemolytic streptococci recovered from infected wounds and from cases of puerperal sepsis were identical with those found in the throats of members of the surgical or obstetrical staffs. The fact that wound infections caused by the hemolytic streptococci are most frequent in the spring, when the percentage of carriers is highest among the operating room personnel, is offered by Meleney<sup>20</sup> and Walker<sup>33</sup> as additional evidence in favor of the nose and throat of operating room personnel as the source of these infections. Hart and Schiebel<sup>18</sup> go so far as to say that organisms from this source are the cause of most surgical wound infections. Many authors have emphasized the importance of nasal and pharyngeal organisms in the spread of contagious diseases, puerperal sepsis, cross infections in pediatric wards, and as the cause of surgical wound infections.<sup>7, 8, 23, 26, 28, 32, 33, 40, 41</sup>

The attempts made by surgeons to prevent contamination of wounds with bacteria from the respiratory tract have been of two kinds: (1) attempts to prevent the escape of bacteria from the nose and throat by the use of masks and (2) attempts to destroy bacteria after their escape from the nose and throat but before they have reached the wound by radiating the air with ultraviolet light<sup>17</sup> or by introducing germicidal aerosols into the air.<sup>35</sup> The latter efforts were foreshadowed by the use of germicidal sprays in Listerian days.

The use in operating rooms of ultraviolet light or germicidal aerosols is comparatively recent, but masks have been employed since Mikulicz,<sup>31</sup> stimulated by the work of Flügge, advocated covering the nose, mouth, and beard with muslin. A great variety of masks have been described, but all of them can be placed in one of two groups: (1) porous masks

designed to filter bacteria out of the air as it passes through them; (2) impervious masks designed to deflect the air stream away from the object to be protected.

A review of the literature reveals many conflicting opinions of the value of either type of mask as a means of preventing the spread of bacteria from the wearer into the air or the inhalation of bacteria from the air by the wearer. It is not practical to review all of the literature, but the following statements summarize the opinions which have been expressed most frequently:

1. The routine use of ordinary gauze masks is of definite value in the control of surgical wound infections, epidemics of puerperal sepsis, and cross infection in contagious disease wards.<sup>5, 6, 23, 28, 40, 41</sup>

2. The routine use of ordinary gauze masks is of little value in checking epidemics of contagious diseases,<sup>22</sup> and, in spite of careful masking, many bacteria escape from the nose or throat and contaminate the air of the operating room. These organisms are responsible for the majority of wound infections.<sup>14-18</sup>

3. The common surgical masks made of a few layers of gauze, under experimental conditions at least, have little power to filter bacteria from the expired air if the wearer talks or coughs.<sup>2, 9, 22, 25, 38, 41</sup>

4. Masks made from many thicknesses of fine mesh gauze<sup>4, 9, 23, 38, 41</sup> or from closely woven material, such as dimity,<sup>2</sup> those containing a layer of rubber or celluloid between several layers of gauze,<sup>2, 3</sup> and simple deflecting masks made entirely of impervious material<sup>39</sup> are highly effective.

5. The gauze masks described above are so difficult to breathe through that air escapes at the sides of the mask. This, of necessity, occurs with masks containing impervious material, and in spite of the claims of those who advocate these masks, the air escaping at the sides is not sterile.<sup>1, 22</sup>

#### DROPLETS AND DROPLET NUCLEI

Wells and his collaborators<sup>13-16</sup> have emphasized the fallacy of judging the presence or absence of air contamination solely by the number of colonies developing from organisms which have fallen upon exposed Petri plates. In their important studies on air-borne infection these workers demonstrated that at least two mechanisms operate. The first involves the commonly understood droplet. These droplets, which vary in size from 0.1 to 2 mm.,<sup>43</sup> are heavy enough to fall rapidly. Since they fall rapidly to the floor, their direct range of infectivity is usually less than 15 feet.<sup>10, 11</sup> The bacteria contained in these large droplets are readily recovered upon exposed Petri plates and this method may be used to estimate the number of droplets falling on a given area. The second mechanism operating in the spread of air-borne infections involves the droplet nucleus. When a droplet is expelled into the air, it falls toward the ground with varying speed, depending on its size and

specific gravity, the presence or absence of air currents, the relative humidity, the speed of ejection, and a number of other factors.<sup>20, 43, 45, 46</sup> Many small droplets evaporate before settling to the ground, leaving tiny buoyant nuclei of particulate matter, the droplet nuclei. The mass of these nuclei is so small in proportion to their surface area that they do not fall to the ground but remain suspended in the air and are wafted about for indefinite periods of time.<sup>43</sup> Some of the droplets expelled from the mouth in talking are so small that they may be considered, for practical purposes, to be droplet nuclei. These droplet nuclei are capable of traveling great distances and may well represent an important means of spreading infectious diseases.<sup>25, 46</sup> Since the droplet nuclei do not fall to the ground, the bacteria contained in them cannot be recovered upon exposed Petri plates. It has been shown that Petri plates will remain nearly sterile when exposed in a room where the air is heavily contaminated with bacteria in the form of droplet nuclei.<sup>46</sup>

It is obvious that any experiments designed to test the efficacy of face masks should be planned to record their power to prevent the passage of both droplets and droplet nuclei. All of the previous studies on masks, except that of Arnold,<sup>1</sup> are incomplete in this regard since the experimenters relied entirely upon the failure of bacteria to fall upon Petri plates as evidence that they did not pass through or around the masks.

The obvious contradictions in the literature,<sup>22</sup> the neglect of all workers except Arnold<sup>1</sup> to enumerate the bacteria which remain suspended in the air, the recent development by Wells<sup>42</sup> of a simple apparatus for recovering the droplet nuclei from a given volume of air, and the present lively interest in transmission of infection through the air led us to undertake a study of masks.

#### MATERIALS AND METHODS

A. *Apparatus*.—An airtight chamber measuring 36 by 26 by 16 inches was constructed (Fig. 1). One side of the chamber was fitted with a rubber diaphragm through which the head of the subject could be inserted. Inlets for filtered sterile compressed air were located above and below the diaphragm. The opposite side of the chamber contained an airtight door through which Petri plates could be introduced. Glass observation panels were placed on the two remaining sides. In the floor of the chamber a connection for a Wells air centrifuge was installed.<sup>42</sup> This instrument consists of an electric motor which rotates a tube lined with agar culture medium. A given quantity of air can be made to pass through the tube in such a manner as to impinge microbes on the agar-coated walls. After forty-eight hours of incubation the colonies are counted. The count is a fairly accurate measurement of the number of organisms per given volume of air. The negative pressure within the chamber, created by the centrifuge, was equalized by the introduction of appropriate amounts of filtered sterile com-

pressed air through the inlets above and below the head of the subject. To regulate this, a water manometer was attached to one side of the chamber. A 15-watt General Electric ultraviolet sterilizing lamp was installed in the roof of the chamber to sterilize the air between tests. It was also used to minimize contamination during certain phases of the tests.

B. *Media*.—Blood agar, beef-heart infusion agar, and meat infusion agar were used, all in significant numbers. Inasmuch as no numerical differences were found, infusion agar was employed almost exclusively, except for the frequent use of blood agar as an indicator to reveal the types of organisms present.

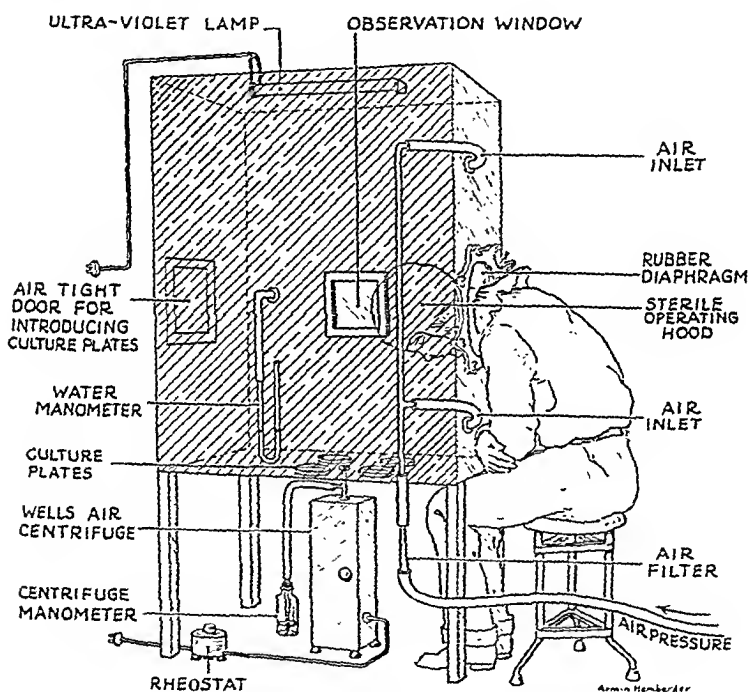


Fig. 1.

C. *Masks Tested*.—These included six types of surgical masks in common use in various hospitals. Some of these were plain six- or eight-ply gauze masks, while others had rubber or celluloid shields between the layers of gauze, as recommended by Blatt and Dale<sup>2</sup> and Walker.<sup>35</sup> The gauze used in these masks did not contain fewer than 32 by 28 threads to the inch when new. After the masks had been laundered several times the mesh became considerably finer due to shrinkage. Although they varied somewhat in design, all of the masks were large enough to cover adequately the nose, mouth, chin, and cheeks. Adjustable metal strips were employed in some of the masks to ensure a snug fit over the nose. In one instance the mask was incor-

porated in the hood which covered the head, face, neck, and shoulders, and left only the eyes exposed. Two widely sold commercial masks were also tested. One of these was an impervious paper mask, and the other contained a special cellulocotton filler between layers of fine gauze. In addition to the surgical masks, three industrial respirators were tested.\* Many of the masks were tested after having been worn in the operating room from one to four hours.

D. *Subjects*.—Forty-one different subjects were used, most of them more than once. They included doctors, nurses, medical students, and laboratory technicians, all accustomed to wearing masks.

E. *Procedure*.—

1. *Control*: The rubber diaphragm was sealed and the door closed. The sterilizing ultraviolet lamp was turned on and left on for fifteen minutes, at the end of which time four Petri plates were placed in the chamber surrounding the centrifuge intake. Twenty cubic centimeters of melted meat infusion agar were then poured into a Wells tube, which was placed in the centrifuge. The centrifuge was turned on and the speed was regulated so as to draw a constant amount of air (23 cubic feet in fifteen minutes) through the centrifuge. The ultraviolet light, which had been left on during these procedures, was now turned off, and the negative pressure created within the chamber by the centrifuge was compensated by the continued introduction of compressed sterile air in amounts adequate to maintain the pressure within the chamber at atmospheric level. At the end of fifteen minutes the centrifuge tube and plates were removed. This constituted a check on the sterility of the incoming air, the efficacy of the ultraviolet light, and the integrity of the system. The tubes and plates rarely contained over a total of five colonies, usually one or two, and frequently none.

2. *Tests on Subjects*: The subject's head was covered with a clean bathing cap. A sterile hood was placed over this. The hood covered the head, neck, ears, and shoulders but left the central portion of the face exposed. The ultraviolet light was turned on, and the seal on the diaphragm removed. The diaphragm and the hands of the subject and operator were cleansed with 70 per cent alcohol and the subject's head was introduced carefully into the chamber through the diaphragm. The snug fit of the diaphragm around the neck of the subject sufficed to maintain an airtight system. The procedure from this point was similar to that of the control test. Four fifteen-minute tests were made with each subject. These were (a) quiet breathing without a mask; (b) talking without a mask; (c) quiet breathing with a mask; (d) talking with a mask.

A second control test of the system routinely followed (b) because in this phase the greatest contamination occurred. Between each phase the chamber was sterilized by means of the ultraviolet light. The sub-

\*The industrial respirators tested were the Dustfoc Respirator of the Mine Safety Appliances Company, the American Optical Company Dust Respirator, R-9100, and the Wilson Products, Inc., Industrial Respirator No. 750, slightly modified.

ject always talked and breathed directly at the plates and centrifuge intake. Controls on two possible sources of contamination other than the respiratory tract were required. These sources were the introduction of the subject's head and the introduction of the plates. Numerous special controls on these two possible sources of contamination proved them to be of negligible importance.

In about one-fourth of the tests the experimental order was altered. The masks were used during the first two phases of the experiment, and the subject was tested without a mask during the last two. This was done to make certain that the variations observed in the four tests were real, and that they were not the result of the experimental order. In other words, did talking or wearing a mask for fifteen minutes affect the respiratory tract in such a way that the number of bacteria expelled subsequently would be increased or decreased? Because many individuals breathe through the mouth while wearing a mask, a series of control tests was conducted with the subject breathing quietly through the mouth rather than through the nose. Neither the sequence of the tests nor the act of breathing through the mouth instead of the nose had any influence on the results. In eight tests the entire floor of the chamber was covered with Petri plates. This required twenty-four plates. By computing the total area of the twenty-four Petri plates and the area of the floor, the total plate count could be translated into an estimated total number of droplets falling on the entire chamber floor. The averages of the four central plates surrounding the centrifuge intake was compared with the averages of the entire twenty-four plates, and it was found that no significant difference existed. It was discovered that while four plates could be introduced without contaminating the chamber, the introduction of twenty-four plates could not be accomplished aseptically. Because of this, and also because of the expense and trouble involved in the use of twenty-four plates, their use was discontinued, and the total count of four plates was corrected so as to represent the total floor area. This corrected total is the value used throughout the data.

F. *Bacteria*.—*Staphylococcus albus*, *Staph. aureus*, *Micrococcus catarrhalis*, *Streptococcus nonhemolyticus*, *Str. viridans*, diphtheroids, gram-positive aerobic bacilli, and other bacteria were recovered. No accurate protocols were kept with regard to types of organisms, because the study was primarily concerned with a quantitative determination of the efficiency of masks.

G. *Tests*.—Over 100 tests were made, plus many special tests, to check the various possible sources of error mentioned above. Of these tests 44 were selected for tabulation as satisfactory from the point of view of controls, inclusion of all phases, etc. (Table I).

H. *Data*.—The data were checked statistically and found to be significant.\*

\*We are indebted to Dr. J. H. Watkins, of the Department of Public Health, Yale University School of Medicine, for assistance in the statistical evaluation of our data.

TABLE I\*

	TUBE COUNT (INDIRECT CONTAMINATION)		PLATE COUNT (DIRECT CONTAMINATION)	
	AVERAGE	MAXIMUM	AVERAGE	MAXIMUM
<i>Surgical Masks</i>				
Quiet breathing without mask	8	20	78	259
Quiet breathing with mask	19	99	91	315
Talking without mask	54	337	3,247	47,600
Talking with mask	35	120	194	620
<i>Industrial Masks</i>				
Quiet breathing without mask	4	15	20	65
Quiet breathing with mask	5	15	22	44
Talking without mask	31	62	1,089	4,200
Talking with mask	7	32	61	130

\*Included in the table are only 30 tests of surgical masks and 14 tests of industrial masks. These tests are complete in all phases. Sixty additional satisfactory tests are not tabulated because the uniformly low counts in quiet breathing with or without masks caused us to omit those phases. The values in the talking phases of the tests are in every way similar to those tabulated above.

#### INTERPRETATION OF DATA

For each of the four tests given (namely, quiet breathing with and without a mask, talking with and without a mask) two values were obtained. The Wells centrifuge tube counts reflected general atmospheric contamination by the tiny droplets and droplet nuclei which did not fall to the floor of the chamber. This has been termed indirect contamination. The plate counts represent the number of heavy droplets which fell upon the Petri plates. This is direct spray contamination as toward an operative field and has been termed direct contamination.

#### RESULTS

*Quiet Breathing and Talking Without Masks.*—Two well-known facts re-emphasized by this investigation were: (a) the small number of bacteria escaping from the respiratory tract during quiet breathing without a mask and (b) the great increase over this number produced by talking. In quiet breathing without a mask, through either the nose or the mouth, indirect contamination was always less than 20 colonies, and averaged 8 colonies; direct contamination was always less than 260 colonies and averaged 78 colonies. In talking without a mask indirect contamination was much higher, averaging 54 colonies with top values of 337 colonies; direct contamination was tremendously increased, averaging 3,247 colonies with occasional top values of 47,000.

*The Effect of Masks.*—A rather unexpected finding was an increase in the number of bacteria expelled by certain individuals during quiet breathing when masks were worn. Indirect contamination was increased by surgical masks in 69 per cent of the tests and by industrial respirators in 43 per cent of the tests (averages: without masks, 8 colonies; with surgical masks, 19 colonies). Direct contamination was increased by surgical masks in 62 per cent of the tests and by indus-

trial respirators in 57 per cent of tests (averages: without masks, 78 colonies; with surgical masks, 91 colonies).

On the other hand, masks were able to reduce the large numbers of bacteria expelled during talking to reasonable levels. Surgical masks decreased the indirect contamination in 65 per cent of the tests, while industrial respirators reduced it in 100 per cent of the tests (averages: without masks, 54 colonies; with surgical masks, 35 colonies). Surgical masks reduced direct spray contamination in 89 per cent of the tests, while industrial masks accomplished this in 100 per cent of the tests (averages: without masks, 3,247 colonies; with surgical masks, 194 colonies).

The actual numbers of bacteria expelled during 44 representative tests are given in Table I.

*Effect of Individual Variation:* Different individuals, unmasked, exhibited marked variations in the number of bacteria they expelled. This was manifest chiefly in the talking tests and is probably correlated with the manner of speaking, shape of the mouth, respiratory tract flora, etc. It emphasizes the need of employing a large number of subjects.

*Other considerations.*—No significant differences were noted when the masks had been worn from one to four hours preceding the tests. No significant differences were noted among the eight types of surgical masks, although a larger series of experiments with each type might reveal moderate differences. The industrial respirators seemed to be somewhat more effective than the conventional surgical masks, although the difference was not striking.

#### DISCUSSION

The results of these experiments indicate that contamination of the air by bacteria from the nose and throat frequently is lowest when unmasked individuals breathe quietly through either the nose or the mouth. Wearing of masks increases, in many instances, the number of bacteria that an individual expels during quiet breathing. While the exact cause of this increase is not clear, it may be due to the increased nasal secretion which masks cause in many individuals. If absolute silence could be maintained in the operating room, the use of masks would not be necessary. In practice this presents certain difficulties. Pool and Bancroft<sup>34</sup> have shown, however, that the use of signals will minimize the amount of speech required in the operating room, and Riese<sup>35</sup> has advocated a silent operating room routine. Inasmuch as absolute silence in the operating room may not be practical, precautions must be taken to prevent the escape of bacteria from the mouth during the act of talking. It is for this purpose that masks have their greatest value. During talking surgical masks reduced the direct spray contamination in 89 per cent of the present tests but did not eliminate it. Surgical masks reduced the indirect or droplet nuclei contamination

in only 65 per cent of the tests, but since the total number of bacteria expelled in the form of droplet nuclei is far less than the number expelled as droplets, this is not of great significance.

There are several reasons for the failure of surgical masks to restrain all the bacteria. In the first place, it has thus far been impossible to construct a filter capable of preventing the passage of all bacteria without making it so resistant to the passage of air that breathing through it is arduous.<sup>21</sup> In the second place, it is difficult to fit a mask to the face in such a way that air does not escape around it. These two difficulties are accentuated in most surgical masks as the gauze customarily used in their construction is a poor filter and they are frequently so small that they cannot be made to fit the face properly.

The commercial respirators are superior to the average surgical mask probably because they contain more efficient filtering material and are designed to fit the face snugly. If properly used, they undoubtedly provide fairly efficient protection. Unfortunately, these respirators possess certain faults which will probably prevent their adoption for use in the operating room. They are uncomfortable to wear and are difficult to sterilize. It is absolutely essential that these respirators fit the face snugly, for if air escapes about the sides, they become dangerous sources of contamination. The problem of maintaining the respirator tight against the face is made difficult by the fact that they are being used for a purpose which is exactly the opposite of that for which they were designed. In industry these respirators serve to prevent the inhalation of dust from the air, while in surgery their purpose is to prevent the escape of bacteria into the air. As the industrial worker inhales, the resistance offered by the filter to the passage of air results in the development of negative pressure within the respirator. This allows the atmospheric pressure to press the respirator more closely to the face. The worker then exhales freely through a valve. On the other hand, with the valve reversed, the surgeon exhales through the filter and its resistance to the passage of air allows a positive pressure to develop within the mask which tends to blow it away from the face. The avoidance of talking, then, is the most practical method yet devised to prevent the escape of bacteria from the nose and throat. This, so far as it is possible, together with the use of efficient masks to guard against the contamination produced by occasional necessary remarks will serve to reduce contamination of the air from the nose and throat to a low level.

#### SUMMARY AND CONCLUSIONS

1. A method of testing masks under conditions of actual use is presented.
2. An unmasked individual breathing quietly through either the nose or mouth expels only a few bacteria into the air.
3. When an unmasked individual talks, he expels large numbers of bacteria into the air.

4. The direct spray contamination of talking is greatly reduced by wearing a mask but is still higher than that of quiet breathing without a mask.

5. Conventional surgical masks are grossly inadequate, as they allow large numbers of organisms to escape through or around them.

6. The avoidance of talking is, at present, the most satisfactory method of preventing the escape of bacteria from the nose and throat of members of the operating room staff.

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# A METHOD TO FACILITATE PROMPT RECOGNITION OF AN ESOPHAGEAL DIVERTICULUM AT THE TIME OF OPERATION

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**B**ECAUSE of the relationship, size, and location, it is not always the easiest matter to recognize certain types of esophageal diverticula as they present themselves through the incision in the neck at the time of operation.



Fig. 1.—A reconstruction of a diverticulum, using two pieces of human esophagus. The diverticulum was injected with methylene blue solution. One can readily see the contrast between the normal esophagus and the stained diverticulum.

I saw a patient who had submitted to two different operations for the cure of the same pulsion diverticulum. The fact that the diverticulum was not corrected at the first operation was obviously due to failure to recognize the sac in its entirety. Because of this experience, the thought

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suggested itself that, if some method could be utilized to render the diverticulum more visible or more easily recognized and its extent and point of severance more readily identified, a forward step would be realized in surgery in this locality.

With this in mind, a patient with a small pulsion diverticulum of the esophagus was given, just prior to operation, 2 dr. of a strong solution of methylene blue, approximately 2 to 5 gr. to the dram. This was instilled on the back of the tongue with a medicine dropper. The patient was instructed to swallow the fluid and to take nothing additional by mouth. The operation proceeded. The esophagus was exposed and the diverticulum, which contained the methylene blue solution that had been swallowed, sprang into view as if it had been electrically illuminated. The sac was easily recognized and outlined. The base as it sprang from the esophageal lumen was promptly grasped and severed. One knew that the severance of the entire sac had taken place and the location thereof because of the vividness of the color of the interior of the esophageal wall after excision. The stump was properly dealt with and the operation proceeded without further ado.

This method has proved valuable in dealing with diverticula in this locality. It is an assurance not only to the surgeon, but also to the patient, that the entire diverticulum is corrected, because of the ease with which it is made visible by the methylene blue instillation.

# THE INCIDENCE OF APPENDECTOMY

## IN FOUR UNRELATED POPULATION GROUPS

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WANGENSTEEN<sup>1</sup> has stressed the importance of appendicitis as a public health problem. In 1935 there were 16,142 deaths from this disease in the United States (mortality statistics, U. S. census). The same source of statistics indicates that, when the younger age groups are considered, appendicitis is found to be uniform throughout these years as one of the agents of death which exacts a high toll. In 1935 it ranked as the fifteenth most important cause of death, including all ages.

Collins<sup>2</sup> reported upon the incidence of appendectomy in the United States Army and Navy for two periods as follows: U. S. Army, 1908-1912; 3.1 per 1,000; and 1933-1935, 10.1 per 1,000; U. S. Navy, 1908-1912, 5.1 per 1,000; and 1933-1935, 13.7 per 1,000. These figures represent selected classes with respect to age, sex, state of health, and availability of surgical service. Many reports from hospitals are recorded, but these are selected as to state of health, and in addition such records have no data on population to which the operations can be related for the computation of rates and therefore give little indication of the number of operations that occur in the general population.

Collins,<sup>3</sup> reporting on the frequency of surgical procedures among 9,000 families, disclosed removal of the appendix as the third most frequent operation performed (5.24 per 1,000).

Because appendicitis is such a common and serious disease, and because the number of physicians specializing in surgery and the number of major operations being performed annually is greatly increasing, it was thought desirable to know how many persons have been appendectomized in some groups of the general population.

### SOURCE AND NATURE OF DATA

The data are from nonhomogeneous groups collected by means of investigation forms<sup>4</sup> which were developed from experience, consequently with accompanying errors inherent in trial-and-error methods. The data as collected were limited to the individual's age at the time of interview, the sex, and whether or not the person had had appendicitis; and, if appendectomized, the age at the time of the operation, the number of attacks prior to the time of the operation, and the results attending appendectomy. A total of 27,242 persons were canvassed from four unrelated groups of the general population.

A. *CCC Personnel Seventh Corps Area*.—The cases analyzed in this group were collected from the Minnesota-North Dakota district of the

Seventh Corps Area, Fort Snelling, Minn., from Dec. 9, 1935, to March 16, 1936. All data were secured through the willing cooperation of Lt. Col. J. W. Sherwood, M. C., District Surgeon, now located at Fort Slocum, N. Y., to whom grateful acknowledgment is made. Questionnaires were addressed to camp surgeons who made the necessary investigations. The care and accuracy which uniformly characterized the completed reports are worthy of special acknowledgment to all those concerned.

In this group of 10,589 persons the ages ranged from 16 to 71 years, 9,637 enrollees being from 16 to 30 years of age. From this group 539 appendectomies were reported; approximately 52 per cent were operated upon following the initial attack, 21 per cent had suffered one previous attack, and 27 per cent had more than three attacks prior to appendectomy (Table I). There were 9,809 persons without a record of appendicitis (92.6 per cent); 780 (7.4 per cent) had a history of diagnosed appendicitis; of these, 539 (5.1 per cent) were appendectomized, or 69.1 per cent of the group with appendicitis.

TABLE I

PERCENTAGE DISTRIBUTION, ACCORDING TO GROUPS, OF ATTACKS OF APPENDICITIS PRIOR TO APPENDECTOMY IN 2,330 CASES

NO. OF ATTACKS	1	2	3-10	MANY	INNU- MERABLE	DATA IN- COMPLETE
CCC personnel	52.0	21.0	22.0	4.0	1.0	—
Hospital admissions	39.3	9.1	21.1	7.0	5.0	18.5
Nurses	55.8	30.2	14.0	—	—	—
School group	60.3	10.8	27.4	1.6	—	—
Combined groups	51.8	17.8	21.1	3.2	1.5	4.6

*B. School Children.*—Eight thousand nine hundred and eighteen school children were interviewed. One group of 880 persons reported individually on forms supervised by the teacher, the school nurse, or the parent. In another group of 8,038 school children the data were collected on forms by the teacher. Both methods proved satisfactory for the purpose intended.

In the Waterloo, Ia., group of 8,038 persons, aged 5 to 20 years, 3,921 were females, 107 of whom reported an appendectomy; 4,117 were males, 95 of whom reported an appendectomy. In the Cedar Falls, Ia., group of 880 the females numbered 460 with 12 appendectomies, and 420 males reported 8 appendectomies. In the entire group 435 (4.9 per cent) instances of appendicitis occurred; of these, 213 (48.9 per cent) were treated by measures other than appendectomy.

*C. Hospital Group.*—In this group 7,585 hospital patients were interviewed by clinical clerks. The group has been treated as combined sexes, as unfortunately a large portion of the data was collected without distinction as to sex.

Of this selected group, 5,469 gave no history of appendicitis, while 2,116 (28 per cent) had had appendicitis, of whom 1,526 (20.2 per cent)

had been appendectomized; however, 106 appendectomies were incidental to some other abdominal operation. In this group 590 cases of appendicitis were treated without operation.

*D. Nurses.*—A group of 150 nurses at the University of Minnesota Hospitals reported 46 instances of appendicitis; 43 had been appendectomized (28.7 per cent).

#### NUMBER OF ATTACKS PRIOR TO APPENDECTOMY

Table I indicates that over one-half of 2,330 persons operated upon for appendicitis were operated upon after the first attack and over one-fifth suffered three to ten attacks prior to appendectomy. Although the data are incomplete, it can be pointed out that appendicitis manifests itself first, in many instances, several years before appendectomy; therefore, the specific age incidence of the disease is not accurately represented by the age at the time of appendectomy.

TABLE II

NUMERICAL DISTRIBUTION BY AGE GROUPS OF APPENDECTOMIZED INDIVIDUALS IN FOUR UNRELATED GROUPS OF WHITE PERSONS

AGE GROUP	SCHOOL GROUP			CCC CAMPS			HOSPITAL GROUP			NURSES		
	NO. INTERVIEWED	NO. OF APPENDECTOMIES	PERSON-YEARS OF OBSERVATION	NO. INTERVIEWED	NO. OF APPENDECTOMIES	PERSON-YEARS OF OBSERVATION	NO. INTERVIEWED	NO. OF APPENDECTOMIES	PERSON-YEARS OF OBSERVATION	NO. INTERVIEWED	NO. OF APPENDECTOMIES	PERSON-YEARS OF OBSERVATION
All ages	8,918	222	102,602	10,589	539	242,762	7,541	1,482	284,695	150	43	3,305
0-4 yr.			44,581			52,931	128	1	37,387			750
5-9 yr.	3,272	39	36,563			52,780	111	4	36,685			743
10-14 yr.	3,870	101	18,888			52,430	121	3	35,784			715
15-19 yr.	1,774	81	2,569	3,665	162	47,927	566	54	33,327	14	3	659
20-24 yr.	2	1	1	4,902	231	19,105	869	149	28,386	93	26	317
25-29 yr.				1,070	81	6,267	696	168	24,122	34	12	89
30-34 yr.				121	13	4,187	685	175	20,567	7	1	24
35-39 yr.				187	13	3,415	639	178	17,453	1	-	7
40-44 yr.				306	12	2,174	615	210	14,794	1	1	1
45-49 yr.				214	20	1,015	660	174	12,155			
50-54 yr.				70	3	341	617	123	9,457			
55-59 yr.				34	2	133	559	101	6,896			
60-64 yr.				15	2	44	515	75	4,646			
Over 65 yr.				5	0	13	760	67	3,035			

#### FREQUENCY OF APPENDECTOMY IN THE WHOLE GROUP OBSERVED

The basic data used in this study are given in Table II. The numbers in some age groups are too small to indicate dependable age variations, but are included for reasons of completeness.

In each instance the person interviewed observed certain experiences over a period of years up to the time of questioning. The 27,198 persons represent a total of 633,364 person-years of observation. The frequency distribution, by age groups, of 2,286 appendectomies as found in 27,198

persons is shown in Table III. The greatest number of appendectomies occurs in the decade from 15 to 24 years.

TABLE III

FREQUENCY DISTRIBUTION BY AGE GROUPS OF 2,286\* APPENDECTOMIES OCCURRING IN 27,198 WHITE PERSONS

AGE GROUP	COMBINED GROUPS	HOSPITAL* ADMISSIONS	CCC CAMPS	NURSES	SCHOOL GROUP
All ages	2,286	1,482	539	43	222
0-4 yr.	32	8	11		13
5-9 yr.	181	41	48	3	89
10-14 yr.	309	110	99	10	90
15-19 yr.	563	310	211	11	30
20-24 yr.	418	281	120	17	
25-29 yr.	243	218	25		
30-34 yr.	171	162	8	1	
35-39 yr.	122	113	8	1	
40-44 yr.	106	101	5		
45-49 yr.	66	62	4		
50-54 yr.	42	42			
55-59 yr.	25	25			
60-64 yr.	7	7			
Over 65 yr.	2	2			

\*In 44 cases the age at the time of appendectomy was not recorded and these 44 cases, therefore, have not been included in these data.

For the total 633,364 person-years of observation there were 2,286 appendectomies, an annual rate of 3.61 operations per 1,000 persons interviewed. The age incidence shows two peaks (Table IV), one be-

TABLE IV

INCIDENCE OF APPENDECTOMY AMONG PERSONS OF DIFFERENT AGES IN FOUR WHITE POPULATION GROUPS

(ANNUAL OPERATION RATE PER 1,000)

AGE GROUP	COMBINED GROUP	HOSPITAL ADMISSIONS	CCC GROUPS	NURSES	SCHOOL GROUP
All ages	3.61	5.21	2.22	13.01	2.15
0-4 yr.	0.24	0.21	0.21		0.29
5-9 yr.	1.42	1.12	0.91	4.04	2.42
10-14 yr.	2.87	3.07	1.81	13.99	4.76
15-19 yr.	6.65	9.30	4.40	16.69	11.68
20-24 yr.	8.74	9.90	6.03	53.63	
25-29 yr.	7.97	9.04	3.99		
30-34 yr.	6.90	7.88	1.91	40.82	
35-39 yr.	5.84	6.47	2.34	133.33	
40-44 yr.	6.25	6.83	2.30		
45-49 yr.	5.09	5.10	3.94		
50-54 yr.	4.29	4.44			
55-59 yr.	3.56	3.63			
60-64 yr.	1.49	1.51			
Over 65 yr.	0.66	0.66			

tween 20 and 24 years and one between 25 and 29 years. The appendectomy rate for the combined group is included although the groups are not homogeneous. The CCC group and the school group, in a statistical sense, were not selected from the general population and may reasonably indicate the appendectomy rate as it occurs in those groups within the general population.

## COMPLICATIONS ATTENDING APPENDECTOMY

Rea and Kleinsasser<sup>5</sup> reported the end results following removal of an "inactive" appendix, the presence of other lesions causing right lower quadrant pain having been excluded by careful examination. In a series of 143 patients from whom an inactive appendix was removed, 102 replied by letter or were examined in the clinic as to their condition since operation. Continuation of the same or other symptoms was reported by 12, while 73 patients who had been operated upon were well four or more years (78.1 per cent).

In a group of 1,989 appendectomies, 79 per cent of the persons reported complete recovery following appendectomy (Table V). In the

TABLE V  
RESULTS ATTENDING APPENDECTOMY IN 1,989 CASES OF APPENDICITIS

RESULTS	COMBINED GROUPS		HOSPITAL GROUP		CCC CAMPS		NURSES	
	NO.	%	NO.	%	NO.	%	NO.	%
Well	1,567	78.8	1,067	75.1	457	86.9	43	100.0
No relief	4	0.2	4	0.2				
Abdominal pain	117	5.9	84	5.9	33	6.1		
Adhesions	71	3.6	71	5.0				
Enterolysis	12	0.6	12	0.8				
Intestinal obstruction	12	0.6	12	0.8				
Hernia	28	1.4	16	1.1	12	2.2		
Obstipation	6	0.3	6	0.4				
Wound infection	21	1.1	14	1.0	7	1.3		
Peritonitis	7	0.4	3	0.2	4	0.4		
Fistula	9	0.5	3	0.2	6	1.1		
Pyelitis	2	0.1	—	—	2	0.4		
Abscess	5	0.2	—	—	5	0.9		
Data incomplete	128	6.4	128	9.0				
Total	1,989	100.1	1,420	99.7	526	99.4	43	100.0

group of nurses all were well after appendectomy; 10 appendectomies had been performed within a year of the interview, while 26 of them had been performed from five to sixteen years previously. The greatest number (86.9 per cent) remaining well after appendectomy were in the CCC group; whereas, 16 per cent of the hospital group reported residual symptoms, another 9 per cent did not report their state of health.

## COMMENTS

In the heterogeneous group of 27,242 persons appendicitis was reported as occurring in 3,377, or 12.4 per cent (Table VI). Appendectomy was performed in 2,330 cases (8.6 per cent).

The rate of appendectomy for the separate and combined groups was determined on the basis of 633,364 person-years of observation. The average annual rate of appendectomy was found to be 3.61 for the entire group. In 44 instances the age at the time of appendectomy was not recorded; therefore, these cases were not included in the annual rate of appendectomy.

TABLE VI

FREQUENCY DISTRIBUTION OF APPENDICITIS IN FOUR UNRELATED GROUPS (1936-1937)

	HOSPITAL ADMIS- SIONS (ALL AGES)	UNIVER- SITY NURSES (18-40 YR.)	SCHOOL CHILDREN (5-20 YR.)	MINNE- SOTA CCC CAMPS (16-71 YR.)	COMBINED GROUPS (ALL AGES)
No. of persons interviewed	7,585	150	8,918	10,589	27,242
No history of appendicitis	5,469	104	8,483	9,809	23,865
History of appendicitis, no operation	590	3	213	241	1,047
History of appendicitis, appendectomy	1,526*	43	222	539	2,330
<i>Percentage</i>					
No. of persons interviewed	100.0	100.0	100.0	100.0	100.0
No history of appendicitis	72.0	69.3	95.1	92.6	87.6
History of appendicitis, no operation	7.8	2.0	2.4	2.3	3.8
History of appendicitis, appendectomy	20.2	28.7	2.5	5.1	8.6

\*106 appendectomies in connection with other operations.

Seventy-nine per cent of the persons having had an appendectomy reported a complete recovery.

Approximately 48 per cent of the persons appendectomized defer operation until the second attack of appendicitis. In this study 1,047 persons with a history of appendicitis (3.8 per cent) were not appendectomized. Of those treated by appendectomy, approximately 30 per cent had been subjected to the risk of three or more attacks of appendicitis and still harbored the appendix.

In the group of school children 49 per cent were treated by conservative measures, while only 31 per cent in the CCC camps were treated without appendectomy. This difference is not related to the number of attacks of appendicitis, as 60 per cent of the school group were operated upon during the initial attack and 52 per cent in the CCC personnel. Approximately 69 per cent of the entire group with appendicitis were treated by appendectomy.

In this study 12.4 per cent reported a specific diagnosis of appendicitis; 8.6 per cent were treated by operation. By means of simple proportion one calculates from an annual rate of 3.61 appendectomies per 1,000 an annual appendicitis rate of 5.21 per 1,000. This compares favorably with the incidence of 5.24 reported by Collins<sup>2</sup> and 5.99 reported by Sydenstricker.<sup>6</sup> Dauer and Lilly,<sup>7</sup> reporting on regional appendicitis mortality rates for the central northwest geographical area from 1926 to 1929, show a mean rate for all ages of 0.174 per 1,000 population. Rudder<sup>8</sup> reports an average mortality rate of 1.37 in the United States Army during 1933 to 1936.

An average annual appendicitis rate of 5.21 plus an average mortality rate of 1.37 means that on the average each physician will have the appendicitis problem to consider eight or ten times a year.

A more rational view of this important surgical problem is gradually being disseminated. Wilkie<sup>9</sup> for many years called attention to the fact that clinically and pathologically there are two varieties of appendicitis, one of the infectious variety and the other of the obstructive variety (essentially a closed-loop intestinal obstruction).

In this clinic during the past few years a consistent effort has been made by Wangenstein and his co-workers<sup>10-17</sup> to evaluate the significance of the obstructive factor in the genesis of appendicitis by experiments on animals and similar careful observations in man. In general this work substantiates the obstructive factor as the most important and common factor in the etiology of acute appendicitis.

Clinically there do not appear to be any reliable measures by which one can distinguish the pathologic changes within the appendix which are primarily due to an obstructive mechanism with its sequence of events as described by van Zwalenburg and more directly emphasized by Wangenstein and Bowers, or the changes within the appendix attending parietal infection without evidence of an accompanying mechanism of luminal obstruction. The thesis of a primary parietal appendicitis appears to be less likely as further studies<sup>19, 20</sup> have revealed an increasing number of anatomical and physiological mechanisms of appendical lumen obstruction.

A microscopic study of the disposition of muscle fibers at the site of the appendiceocecal union revealed no evidence of a true cecoappendical sphincter. However, a variable number of muscle fibers were found to be blocked on the medial or ileal side of the appendiceocecal union in approximately 60 per cent of 250 specimens examined. Dissection of the taeniae coli at this junction discloses the structural requirements of an irislike diaphragm<sup>21</sup> capable of dynamic or adynamic approximation of the appendical lumen.

In approximately 30 per cent of cecoappendical junctions examined<sup>12</sup> the value of Gerlach and Nanninga's mucosal fold were present and may encourage the stagnation of infected appendical contents by complete or incomplete obstruction of the cecoappendical orifice. This obstructive mechanism is seldom, if ever, ascertained by the surgeon and may well be present in those instances where no evidence of obstruction is found to have been present in the appendix after its removal.

The risk of delaying operation in the hope that parietal appendical inflammation will resolve or that a primary obstructive appendicitis will relent is a procrastination and unwarranted risk which even under observation in a hospital should not be undertaken lightly.

#### SUMMARY

Twenty-seven thousand two hundred and forty-two persons were interviewed; 3,377 gave a history of diagnosed appendicitis; 2,330 were treated by appendectomy.

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An average annual appendicitis rate of 5.21 plus an average mortality rate of 1.37 means that on the average each physician will have the appendicitis problem to consider eight or ten times a year.

# THE SURGICAL SIGNIFICANCE OF ABDOMINAL WALL PAIN

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ABDOMINAL pain is one of the most important symptoms in the practice of medicine, but, because of its subjective nature, it is at times undependable. The variations in individual sensitivity and in individual ability to describe the pain as to severity, duration, location, radiation and its association with other symptoms provide a chance of error which may be eliminated by the elicitation and careful interpretation of tenderness. Misinterpretation of this important sign is responsible for many diagnostic errors, the most common of which is the failure to recognize its existence in the abdominal wall or parietes rather than in intra-abdominal viscera.

We readily consider and detect intercostal neuralgia in the upper chest wall, and yet we commonly fail to consider the possibility or detect the presence of the same condition elsewhere. Any area of the body surface may be involved in this sensory disturbance, and its diagnosis usually depends upon its differentiation from pathologic changes in some underlying viscera. Upper cervical trunk neuralgias have been mistaken for intracranial, mastoid, and sinus lesions. Involvement of the lower cervical and upper thoracic trunks producing a brachial neuralgia have been diagnosed as subdeltoid or subacromial bursitis, sprains, periostitis, bone tumors, and cervical ribs. Neuralgia of the fourth to sixth thoracic trunks may simulate pleurisy and mastitis, and on the left side, cardiac pain, especially when filaments from the fourth trunk entering the brachial plexus may send painful stimuli into the arm. The lower six thoracic spinal nerves and the first two lumbar nerves constitute the entire innervation of the abdominal wall, and involvement of these trunks may simulate lesions of any intra-abdominal viscera.

Because of the greater frequency of spinal injuries and of chronic postural trauma in the lower thoracic spine, neuralgia of the abdominal wall, or parietal neuralgia,<sup>1</sup> is probably the most frequent type. Failure to differentiate an abdominal wall neuralgia from disease of an intra-abdominal viscus accounts for the majority of operative failures in which pain is the chief symptom.

For years we have been taught that pain in the abdominal wall is always a viscerosensory reflex, or a higher sensory neuron manifestation of visceral pain. This phenomenon, first described by Ross<sup>2</sup> in 1888 and during the following decade by Mackenzie,<sup>3</sup> Head,<sup>4</sup> Sherren,<sup>5</sup> and others,

The observed annual appendectomy rate was 3.61 per 1,000.

Seventy-nine per cent of the appendectomized individuals reported a complete recovery.

It is desired to recognize the inestimable assistance of Mrs. Bee Thayer Buirge.

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of his patients over 40 years of age had hypertrophic arthritis of the spine, that 31 per cent of these had evidence of nerve root pressure, and that 25 per cent of these were operated upon for visceral disease without relief of their symptoms. Freedman<sup>16</sup> stresses toxic neuralgias in reporting 42 operations for appendicitis in children during an epidemic of upper respiratory infections. Davis<sup>17</sup> examined 250 boys and girls with abdominal pain and found that only 9 per cent were due to intra-abdominal lesions.

In a study of the correlation between postural trauma and abdominal pain, one of us examined 110 nurses in various stages of training. Forty, or 36 per cent, had some form of spinal abnormality, the most common being a functional scoliosis due to a short leg. Fifty per cent of this group presented evidence of spinal nerve root pressure or irritation demonstrated by a hyperalgesia over the corresponding nerve distribution. The associated neuralgia was twice as frequent in the graduate nurses as in those recently entering training, indicating a definite relationship to postural trauma. Six, or 30 per cent, of those with root symptoms were operated upon for chronic appendicitis, one for cholecystitis and again for adhesions without relief of pain. Later studies in this group revealed no further development of neuralgia in those whose postural defects were corrected early in training.

#### ETIOLOGY

As pointed out by Carnett,<sup>26</sup> Bates,<sup>19, 21</sup> and Goldthwait,<sup>18</sup> the most frequent cause of neuralgia of the abdominal wall is some form of spinal abnormality causing inflammation about, or actual pressure on, the spinal nerve root. The structural scolioses, injuries, disease, and tumors of the spine constitute definite orthopedic problems, and root symptoms, when present, are readily recognized. The accentuated or loss of lumbar lordosis,<sup>21</sup> the spinal strain of a fat-weighted abdomen,<sup>22</sup> and functional scolioses that usually escape the orthopedic surgeon constitute the majority of so-called postural neuralgias. These mild functional scolioses are most commonly compensatory to a tilted pelvis due to a short leg.<sup>20</sup> Because of the absence of backache or a limp, this may go unnoticed, and, when recognized, its significance may be overlooked.

The articular facets which form part of the intervertebral foramen are nearly vertical in the lumbar region and impinge more forcibly upon one another in lordosis. This strain of the articular processes has been shown by Goldthwait and others<sup>18</sup> to produce a chronic inflammatory reaction with definite irritation to the emerging nerve trunks either from the inflammatory reaction or from actual bony narrowing of the foramen. In scolioses they may impinge only on the concave side of the curvature and, therefore, in a compensatory scoliosis neuralgia may be bilateral, at the concavity of both curvatures, thus producing pain in the left chest and right abdominal wall. The frequent development of a spinal

soon became widely accepted. The zones of somatic reference were described on the basis of embryonic development by Head<sup>4</sup> and later were charted by Elsberg and Nienhof<sup>6</sup> with minor changes in their distribution. Superficial pain in these regions for a time was considered to be diagnostic of lesions of the corresponding underlying viscera. However, the closer clinicopathologic correlation of more recent years has failed to bear out this constant relationship between intra-abdominal lesions and superficial pain, and a state of confusion has developed regarding its significance.

The majority of cases of abdominal wall pain and tenderness are definitely not associated with intra-abdominal lesions. Elsberg and Nienhof<sup>6</sup> erroneously reported a case of Pott's disease with spinal nerve root symptoms as chronic appendicitis with a viscerosensory reflex. Livingston,<sup>8</sup> Cope,<sup>9</sup> and other staunch supporters of the viscerosensory reflex theory admit the "occasional" absence of intra-abdominal lesions at operation, but without explanation for this occurrence.

In discussing the persistence or return of these supposed referred pains postoperatively, Pottenger<sup>10</sup> attributes them to an injury of the sensory neuron by the recent inflammatory lesion, thereby permitting an unphysiologic response to subclinical stimuli. Others attribute them to abdominal wall aponeurotic strains, neuromas, or adhesions. Alvarez and Gibson<sup>11</sup> dismiss them as neurotic manifestations. The willingness with which these patients will submit to operation after operation in a futile attempt to obtain relief from abdominal pain is evidence of a genuine complaint, and the repeated operative failures are sufficient to warrant their becoming neurotics.

We recently examined a "neurotic" woman with a fecal fistula which resulted from an operation for adhesions. She had had three previous operations, an appendectomy, salpingectomy, and cholecystectomy, and continued with her original complaint of pain in the right side of her abdomen. Examination revealed abdominal wall tenderness which was traced back along the eleventh and twelfth thoracic and the first lumbar nerve trunks to the spine where she presented a scoliosis with a superimposed arthritis. This tragedy was unquestionably the result of inadequate or misdirected physical examinations.

#### INCIDENCE

The incidence of intercostal neuralgia of the abdominal wall is far greater than is generally supposed. Carnett<sup>13</sup> considered it responsible for nearly 90 per cent of all gastrointestinal studies proving negative. He estimated that 90 per cent of all cases diagnosed as chronic appendicitis and nearly 50 per cent diagnosed as acute appendicitis were intercostal neuralgia. Bockus<sup>14</sup> found that 7.5 per cent of his private patients had abdominal wall neuralgia and that 44 per cent had laparotomies without relief of pain. Cottrell<sup>15</sup> reported that 44 per cent

the table in order to contract his abdominal muscles thereby protecting the underlying viscera from pressure of the palpating fingers. It should also include vigorously pinching generous folds of skin fascia and fat of the abdominal wall. Comparison with remote regions may be necessary in a suspected bilateral lesion. To avoid possible error in degree of pinching, an extensive fold may be grasped overlying the midline of the abdomen in unilateral lesions.

The tenderness of a true visceral lesion, with the possible exception of peptic ulcer and peritonitis, is decreased or absent to these simple pinch-and-poke tests.<sup>26</sup> The tenderness of an abdominal wall neuralgia, on the other hand, is unmistakable. It is unchanged over a voluntarily tensed abdomen and is readily elicited by the pinch test. It usually extends over a greater area than the actual pain and may involve the entire distribution of the nerve, parts of which may overlap the thorax or extremities. It may be elicited over the involved nerve trunk along its course between the ribs and over or just lateral to the vertebral spine at its level, or only at its terminal distribution on the anterior abdominal wall. Regardless of the intensity of the pain, rigidity is usually absent as the motor fibers are rarely involved.

#### NERVE BLOCK

In a suspected coexisting visceral lesion a successful paravertebral procaine nerve block will eliminate the pain and tenderness of the abdominal wall without influencing that of intra-abdominal origin. In this procedure the patient lies prone with a pillow beneath the abdomen and a skin wheal is produced at the elected site of injection, which in the thoracic region is 4.5 cm. lateral to the vertebral spine of the affected trunk. A 2-inch 20 gauge needle is inserted perpendicularly until its point touches the rib. Its position is then shifted downward and pushed 0.5 to 1 cm. deeper into the intercostal space where, after the usual precautionary measure of withdrawing on the syringe plunger, 5 c.c. of 2 per cent procaine solution is injected. In the lumbar region a 3-inch needle is inserted 3 to 3.5 cm. lateral to the upper border of the posterior spinous process and passed inward about 4 to 6 cm., where it should strike the transverse process. After its depth is ascertained, the needle is partly withdrawn and reinserted upward over the process about 1.5 cm. deeper where the solution is injected. In lower abdominal neuralgias the ilioinguinal nerve may be blocked in its course 1 or 2 cm. above the crest of the ilium, deep to the external oblique fascia. Perforation of this fascia resembles the click of the dura in a spinal puncture, and rigid fixation of the needle point against lateral motion assures its location. In limited terminal neuralgias with little or no trunk tenderness, simple infiltration about the area of tenderness is of value. A successful block is indicated by a brief period of anesthesia of the nerve distribution usu-

arthritis in these cases of chronic postural trauma accentuates the root symptoms and constitutes an annoying therapeutic problem.

The acute, severe abdominal neuralgias may be due to a spinal injury, but they are usually toxic in origin. They accompany or follow acute upper respiratory infections, pneumonia, other infectious diseases, and, rarely, appendicitis or other intra-abdominal visceral diseases.<sup>25</sup> With no apparent consideration of postural trauma Davis<sup>17</sup> considers most neuralgias to be toxic in origin, attributing them to a neurotrophic virus frequently present in common colds and related to that of herpes zoster, suggesting the possibility that zoster is frequently present but seldom herpetic.

Musser lists sixty-six extra-abdominal disorders causing abdominal pain, including all of the toxic, infectious, and traumatic causes of intercostal neuralgia.<sup>33</sup> Tabes dorsalis, plumbism, herpes zoster, black widow spider bite, and diabetic acidosis may cause violent abdominal wall pain.<sup>39, 40</sup>

#### DIAGNOSIS

The diagnosis of abdominal wall or parietal neuralgia is not difficult. In any case of chronic dull abdominal pain, especially with an associated backache, neuralgia should be considered. It must be remembered that the intensity and duration of pain may vary to almost unbelievable limits. It may be a mild soreness or an excruciating pain and may last for a few hours or several years. One sees the apparently normal child whose play is interrupted with a "stitch in the side" which disappears upon resting; the patient with "chronic appendicitis" whose pain recurs postoperatively, and the ptotic, dyspeptic, neurotic with operative scars and a symptom complex which may be traced back through exacerbations and remissions to youth. The persistent mild soreness of a chronic abdominal neuralgia may become an excruciating, stabbing pain of a toxic neuralgia similar in severity to that of a sciatica or tic douloureux and even simulating an intra-abdominal catastrophe.<sup>25</sup> The pain may involve any or all branches of one or more nerves on either or both sides.

Pain, being a purely subjective symptom, is, as previously stated, less dependable than its objective manifestation, tenderness. However, the elicitation of tenderness by merely palpating the relaxed abdomen is of little diagnostic value. It fails to differentiate between pain in the abdominal wall and in the viscera. Because the examining fingers must dip more or less deeply into the abdomen before the relaxed muscles offer sufficient counterresistance to demonstrate the abdominal wall tenderness, the examiner erroneously assumes that the tenderness is therefore deep seated and within the abdomen. Further examination should include palpating or firmly poking against the voluntarily tensed abdomen, having the patient raise his legs or head and shoulders from

of catarrhal or toxic jaundice, all contribute to an incorrect diagnosis. The Murphy test for gall bladder tenderness, elicited by poking upward below the right costal border on inspiration, is always positive in intercostal neuralgia in this area. A constant pain in the gall bladder region unassociated with dyspepsia and unconfirmed by laboratory and x-ray studies is frequently intercostal neuralgia and constitutes the majority of operative failures in chronic cholecystitis.

Due to the anatomical weakness of the lumbodorsal spine, neuralgia of the twelfth thoracic and first lumbar nerves is rather frequent.<sup>32</sup> The fact that it occurs three times more frequently on the right than the left side is due to the higher incidence of a left lumbodorsal scoliosis.<sup>23</sup>

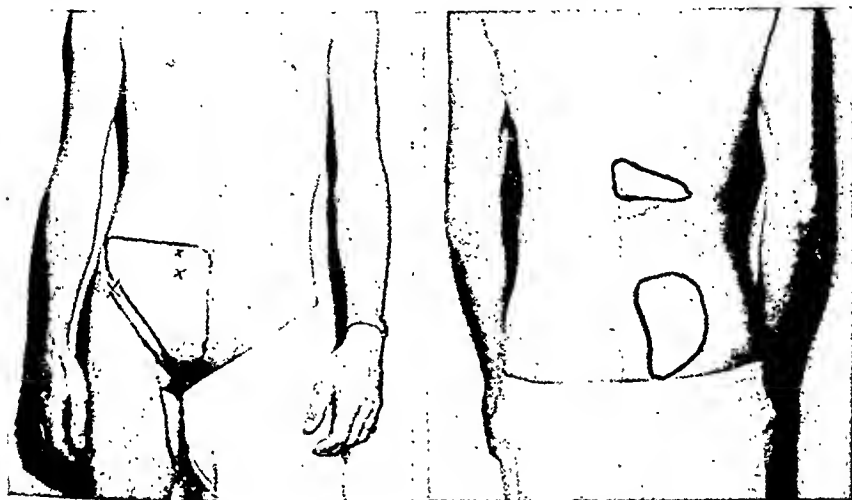


Fig. 2—C.D., a typical case of short left leg functional scoliosis with right twelfth thoracic intercostal neuralgia. The areas of hyperalgesia as here indicated are the nerve trunk and adjacent vertebral spine, the upper medial buttock or sacroiliac region, the right lower abdominal quadrant with maximum pain and tenderness at Valleix point (border of rectus), the area overlying Poupart's ligament, and the upper inner aspect of the thigh. Symptoms of "chronic appendicitis" were not relieved by appendectomy ten years previously. Several attacks of acute right lower quadrant abdominal pain accompanied upper respiratory infections. A back sprain produced pain and tenderness in the sacroiliac regions which was unrelieved by strapping but relieved by twelfth thoracic nerve block. The chronic pain has been relieved, and the acute attacks have been decreased by a heel lift to correct the scoliosis.

The twelfth thoracic and first and second lumbar nerves form the ilio-inguinal and iliohypogastric nerves which supply the lower abdominal wall, and, since they, like the lower six thoracic intercostal nerves, penetrate the external oblique aponeurosis at the outer border of the rectus sheath to enter the rectus muscle, they produce points of maximum tenderness in this region known as Valleix points.<sup>12</sup> On the right side this corresponds approximately to McBurney's point. (Fig. 1.)

The most skeptical persons may usually be convinced of the nerve root origin of this parietal pain and tenderness in the lower right quadrant by exploring the remaining areas of distribution of the ilioinguinal nerve. Tenderness along the inguinal branch may be elicited over the

ally followed within an hour by return to normal sensation, and frequently with the absence of pain and tenderness. In painful trigeminal, brachial, and sciatic neuralgias this is an especially welcome therapeutic measure. The relief from pain often persists for weeks or months in spite of a persistent traumatic, arthritic, or malignant etiology.

#### LESIONS SIMULATED

The asthenic type of ptotic habitus presents a greater incidence of functional scoliosis and other postural defects.<sup>18, 27-29</sup> The associated visceroptosis presents gastrointestinal symptoms which, added to the

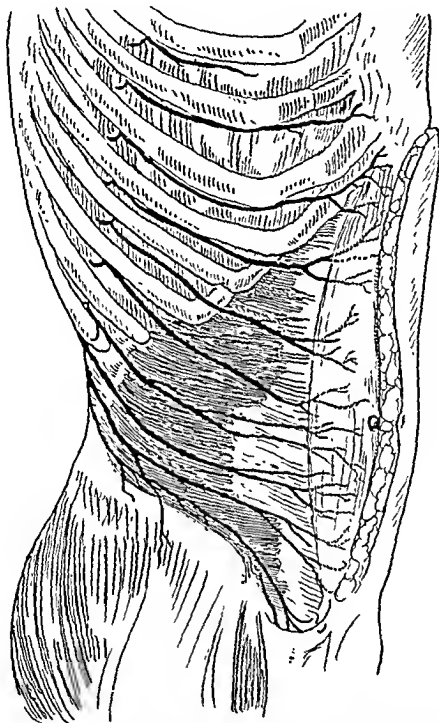


FIG. 1.—Dissection demonstrating the innervation of the abdominal wall by the lower six thoracic and first two lumbar spinal nerves. Their course along the transversalis muscle and their superficial (Vallieux) points of entrance to the rectus sheath are illustrated.

neuralgia, may simulate many intra-abdominal visceral lesions,<sup>30</sup> among which are acute and chronic cholecystitis,<sup>37</sup> appendicitis,<sup>31, 35</sup> and salpingitis, ureteral colic of nephroptosis, and "tugging" peritoneal adhesions.

The upper right quadrant of the abdomen is supplied by the seventh to tenth right intercostal nerves, the involvement of which may simulate many gall bladder or biliary tract symptoms.<sup>37</sup> Pain along the eighth or ninth nerve trunk at the angle of the scapula, visceroptotic epigastric symptoms of an obstructing ligament of Treitz, and a previous attack

## SUMMARY AND CONCLUSION

1. Intercostal neuralgia of any of the lower six thoracic and the first lumbar nerves involves the abdominal wall, and the resulting abdominal pain and tenderness may be referred to as parietal neuralgia.

2. Pain and tenderness of the abdominal wall may be differentiated from intra-abdominal visceral pain by the simple pinch-and-poke tests here described.

3. A viscerosensory reflex is an infrequent cause of abdominal wall pain.

4. Parietal neuralgia accounts for the majority of operative failures in chronic appendicitis, cholecystitis, salpingitis, and other abdominal lesions where pain is the chief symptom.

5. When parietal neuralgia is present, it should be "blocked off" before making a diagnosis of pathology, especially in chronic cases, or in patients with multiple abdominal scars who complain of persistence of their original pain.

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anterior portion of the iliac crest, the inguinal canal,<sup>32</sup> the labia majora, and an area of variable size on the upper inner aspect of the thigh. The iliac branch supplies an area on the upper inner aspect of the buttock overlying the sacroiliac region, where pain and tenderness may be mistaken for sacroiliac strain or arthritis.<sup>33, 34</sup>

Patients with pain and tenderness in the right lower quadrant in the absence of rigidity, fever, and leucocytosis, constitute the majority of operative failures in chronic appendicitis.<sup>35</sup> In the presence of fever and leucocytosis from an upper respiratory infection or pneumonia an operation is hazardous. Many advise against operating for chronic appendicitis in the absence of a previous acute attack.<sup>36</sup> It must be remembered, however, that an acute toxic intercostal neuralgia may have been superimposed upon a chronic intercostal neuralgia,<sup>35</sup> thereby closely simulating an acute attack of appendicitis.

Rigidity is rare in intercostal neuralgia, but it occasionally exists and presents a delicate diagnostic problem; and, of course, the absence of rigidity does not exclude true appendicitis (Fig. 2).

#### COMMENT

The parietal nature of abdominal pain and tenderness in intercostal neuralgia is not always recognized preoperatively and, when recognized, it is frequently attributed to a viscerosensory reflex from a supposed visceral lesion. When the pain recurs postoperatively, it may be attributed to malingering, hysteria, neurosis, further visceral disease, or adhesions. In either of the last two diagnoses the patient may be reoperated upon one or more times and may develop both a neurosis and adhesions.

Since chronic intercostal neuralgia of the abdominal wall is usually aggravated by increased physical activity, it is usually relieved by prolonged bed rest incidental to an operation. It is after the patient has resumed his physical activity and the pain recurs that the correct diagnosis may become apparent. These instances of operative failures are really diagnostic errors resulting from hasty, misdirected, and incomplete physical examinations.

In considering intercostal neuralgia as a possible diagnosis in abdominal pain, one must be careful to rule out any possible intra-abdominal lesions. It would be far better to remove erroneously a normal appendix than to allow a gangrenous appendix to rupture. There is a definite risk, however, in any laparotomy and many unnecessary ones may be avoided by carefully differentiating between intra-abdominal and abdominal wall pain and tenderness.

Treatment of the majority of these cases consists merely of correcting postural defects or spinal injury by the usual orthopedic measures<sup>19, 28, 29</sup> and by the usual medical management of a toxic or infectious etiology.<sup>12</sup>

## SURGERY IN THE CAROTID SINUS SYNDROME

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MANY individuals who demonstrate an abnormality of the carotid sinus reflex as described by Weiss and Baker<sup>1</sup> and called the carotid sinus syndrome suffer only mild symptoms. There are a small number of more severely afflicted patients in whom the characteristic symptoms of vertigo, dizziness, and unconsciousness may be alarmingly dangerous or totally disabling. Surgical denervation of the carotid sinus affords relief in these patients. Since March, 1938, five such operations have been performed on the Third Surgical Division of Bellevue Hospital. The procedures employed in the diagnosis, operation, anesthesia, and the pre- and postoperative care are herewith reviewed.

*Diagnosis.*—The diagnosis of hyperactive carotid sinus was made in all these patients according to the methods described by Weiss. Digital pressure over the bifurcation of the common carotid artery, stimulating the endovascular pressure sensitive fibers in the carotid bulb, produces a train of symptoms similar to the complaints of the patient. Pressure is exerted firmly and for several seconds at a point over the pulsating artery at the level of the upper border of the thyroid cartilage. The patient sits upright and is supported against sudden unconsciousness. A record of pulse rate and blood pressure changes is kept and in our patients electrocardiographic tracings are taken during the manipulation. Both sides are not stimulated simultaneously. An appreciable time interval, at least fifteen minutes after recovery, is allowed to elapse between tests. We have found that one side is always more sensitive than the other. The more sensitive side is denervated. In all the patients, except one, who were submitted to surgery, sufficient pressure produced unconsciousness. The patients are classified, as far as possible, into one of three types: vagal, pressor, or cerebral.

When the main efferent pathway of the reflex is through the vagus nerve, marked bradycardia results. Cerebral anemia which follows the bradycardia causes vertigo, dizziness, sometimes convulsive movements, and unconsciousness. The efferent pathway through the sympathetic produces a fall in blood pressure and cerebral anemia. Unconsciousness is delayed in both these mechanisms and follows a train of symptoms. The cerebral type of reflex causes unconsciousness suddenly, with no change in pulse rate or blood pressure and without intervening

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border of the sternomastoid muscle and is carried through the skin, superficial fascia, and platysma. The deep fascia is made tense by lateral traction on the muscle and incised with care in order to prevent injury to two or three veins which cross the artery to reach the internal jugular vein. These veins may be of alarmingly large size. They should be ligated and cut. With the sternomastoid muscle retracted laterally, the carotid sheath is exposed and the artery may be seen and palpated. The sheath should be opened carefully because the descendens hypoglossi nerve lies on its surface and should be preserved if possible. Location of the bifurcation may be confusing because of the depth of the internal carotid. The superior thyroid artery is a good guide to the level. With complete exposure, the bulbous dilatation of the origin of the internal carotid is easily recognizable. In the bifurcation and just posterior to the inner edge of the internal carotid artery, the carotid body may be seen. It is frequently concealed in areolar tissue and need not be isolated. During the manipulation of the sinus, at this stage, the reflex is stimulated, and the artery may be seen to be pulsating slowly; the blood pressure may drop if the reflex is of the depressor type. The adventitia of the root of the internal carotid may be lifted with thumb forceps and cut. As the dissection proceeds around the circumference of the artery, which may be rotated with a ligature carrier, the section of the adventitia posteriorly\* will be followed by an immediate elevation of blood pressure. This may be evident by the oozing of small blood vessels. Shortly thereafter the pulse rate becomes rapid. The reflex arc is obviously broken. The carotid sheath and deep fascia are sutured in separate layers.

There is no special postoperative care necessary. Occasionally, the rise in blood pressure, which is temporary, may cause unexpected bleeding and cause a hematoma to form, which happened in one of our cases. The patient is allowed out of bed on the second postoperative day.

#### CASE REPORTS

CASE 1.—H. B., male aged 65 years, was first admitted to the hospital in April, 1934. The patient complained of nervousness, loss of weight, palpitation, exophthalmos, and diplopia. A diagnosis of hyperthyroidism was made and a right thyroid lobectomy was performed. He was discharged, June 30, 1934, and was well until December, 1934, when symptoms reappeared; namely, loss of weight, tremor, and palpitation. He was readmitted in March, 1935, and on April 20, 1935, a left subtotal thyroid lobectomy was performed. His symptoms were relieved, and he was discharged May 7, 1935.

He again began to lose weight during October, 1935, and complained of nervousness and palpitation and evidenced one added symptom, tightness of the neck. Medical treatment for three weeks brought about some improvement. The diagnosis at this time was thyrotoxicosis, arteriosclerosis, and hypertension. He attended the Thyroid and Cardiac Clinics and felt well until early in March, 1936, at which time

\*Studies on the cadaver indicate that the nerve separates itself from the adventitia at a slightly higher level and may be cut as it courses along the posteromedial aspect of the internal carotid artery.

symptoms. This latter type is rare; no example is included in this report. In severe cases, where surgical therapy is indicated, the efferent pathway is generally mixed vagal and pressor with vagus effect predominating. The determination of the type of syndrome is important in the preoperative care and the anesthetic management.

Before operation further diagnostic tests are made by blocking the sinus nerve with an anesthetic solution. Ten cubic centimeters of a 1 per cent solution of procaine is injected in the region of the bifurcation of the carotid artery using the transverse process of the fourth cervical vertebra as a guide.<sup>2</sup> When the nerve to the carotid sinus is blocked, pressure over the bulb will produce no symptoms. This will give added assurance that operation will be effective in abolishing the reflex.

*Preoperative Care and Anesthesia.*—The preparation of the patient has been undertaken largely by the anesthesia department. Atropine, scopolamine, and the barbituric acid derivatives suppress the reflex. In those cases in which the vagal slowing is so marked that prolonged asystole may follow operative manipulation, atropine should be administered before operation. Cases in which the blood pressure fall is alarming may be given ephedrine to prevent much of the fall during operation. Morphine has no effect or is an excitor. An attempt is made to avoid complete suppression during operation because of the value to the surgeon of knowing exactly when the nerve has been cut. If the anesthetic agent employed does not depress the reflex, the anesthetist, by recording the pulse and blood pressure changes as they are affected by the operative stimulation of the reflex, may tell the surgeon when the arc has been interrupted. We have found that the nerve emerges from the posterior aspect of the base of the internal carotid artery, but it may be difficult to isolate without a physiologic guide. As ether, vinylene, and chloroform may suppress the reflex during deep narcosis, these drugs are not employed. Nitrous oxide or cyclopropane have little effect or sensitize the mechanism. Cyclopropane is the anesthetic of choice. It permits the use of a respired atmosphere containing a high percentage of oxygen, valuable during cerebral anemia. It is quickly controlled, potent, and permits the convenient employment of the desired technique. The carbon dioxide absorption method is employed for administration, and an endotracheal tube is utilized.

The latter is necessary to assure an airway and to permit the convenient application of artificial respiration when indicated. The anesthetist must make practically continuous determination of the pulse rate and rhythm as well as the arterial tension.

*Operative Procedure.*—The skin is prepared in the usual manner. With the head held in the midline and the neck slightly extended, an incision about 5 cm. long is made with its middle at about the level of the upper border of the thyroid cartilage; the bifurcation of the common carotid artery is described as being at this level, but it may vary two to 3 cm. in different subjects. The incision is placed along the anterior

area about the bifurcation of the right common carotid was infiltrated with 5 c.c. of 2 per cent procaine solution and subsequent pressure produced no reaction.

On March 7, 1938, the patient was operated upon. The right carotid sinus was denervated. He was discharged April 14, 1938, without having had a recurrence of dizzy spells, although the headache persisted with a lesser degree of severity. Pressure over the sinus produced no reaction.

CASE 3.—J. R., male, aged 72 years, was admitted to Bellevue Hospital, March 23, 1938, complaining of an increasing frequency of attacks of dizziness, loss of vision, a feeling that his heart had stopped, and unconsciousness. These attacks occurred at irregular times, occasionally while in bed, but always following sudden movements of the head. He first noticed the onset of these episodes in 1911, when he fell and injured himself. He was brought to a hospital and told that his heart was bad. In 1931 he was admitted to Bellevue Hospital with similar complaints, in addition to which dyspnea and edema of the ankles had developed. He was in the hospital for one month and was discharged improved. *Diagnosis:* Generalized arteriosclerosis, enlarged heart, and auricular fibrillation.

At the time of the present admission, March 23, 1938, his blood pressure was 136/68; the peripheral arteries were tortuous and calcified; pulse was totally irregular with no pulse deficit; the heart was enlarged with no signs of failure. Pressure on the left carotid sinus produced immediately asystole which lasted throughout the period of pressure and the symptoms of dizziness, loss of vision, and the unconsciousness of which the patient complained. He was digitalized, and four days after admission the pulse rate became regular at a rate of 120. Electrocardiographic tracings showed auricular flutter with a 2:1 auriculoventricular block. Pressure over carotid sinus increased to a 20:1 ratio with asystole of 4.16 seconds. The rhythm subsequently varied from fibrillation to flutter.

On April 19, 1938, the patient was operated upon, under cervical plexus block anesthesia, and the left carotid sinus was denervated. During the postoperative period a hematoma developed under the skin and was evacuated on the fifth day. Thereafter healing was prompt. He was discharged May 11, 1938. Pressure on left carotid sinus produced no cardiac slowing or symptoms. On July 14, 1938, the patient was again admitted to the hospital complaining of shortness of breath and swelling of the ankles. There have been no dizzy spells and pressure over the carotid sinus produces no symptoms or cardiac slowing.

CASE 4.—F. R., male, aged 59 years, was admitted to Bellevue Hospital, Sept. 26, 1938, the same day that he had fallen unconscious for a period of about ten minutes. Past history revealed a severe accident in 1934, when he fell six stories and suffered skeletal and head injuries for which he was hospitalized for about six months. During the past two years he has had infrequent attacks of dizziness, ringing in the ears, vertigo, and unconsciousness. His occupation was carpentry, but during the past year he has not worked because he feared that another attack while on a scaffold or ladder would result in severe injury. He realized that he could prevent the unconscious phase of the attack if he could loosen his collar when he first became dizzy.

At the time of admission, it was found that pressure over the right carotid sinus would produce a bradycardia, dizziness, and blurring of vision. Pressure on the left carotid sinus produced some slowing of the pulse. The blood pressure of 160/100 was unchanged by pressure. On Oct. 10, 1938, the region of the right carotid sinus was blocked with 2 per cent novocain solution, and subsequent pressure produced no effect. On Oct. 11, 1938, the patient was given .01 gr. of atropine subcutaneously, repeated in two hours. Subsequent pressure on the right carotid sinus produced slight slowing of the heart but no dizziness, and pressure on the left had no effect.

he complained of loss of weight, tremor, nervousness, palpitation, dyspnea, and dizziness. There were no complaints of choking or constriction of neck at this time. A small, vascularized nodule of thyroid tissue, attached to the left superior pole, was removed surgically in March, 1936. At this operation the superior thyroid artery was ligated proximal to the nodule.

Symptoms returned in October, 1936, and the patient was treated in the hospital, from Dec. 7, 1936, to Jan. 5, 1937, without operation. He was without complaints referable to the thyroid; he had occasional dyspnea on exertion and precordial pain. Early in April, 1937, he had his first attack of unconsciousness, and on April 29, 1937, he had a third similar episode and was brought to the hospital in an ambulance.

It was felt that his general condition was progressively improving and that paroxysmal auricular fibrillation was the etiologic factor causing the fainting spells. He was given digitalis and discharged ten days later on a maintained dose of 1.5 gr. a day. His general condition continued to improve, but he had occasional attacks of unconsciousness lasting ten to fifteen minutes. He also began to notice transient attacks of vertigo brought on by changes in position. It was found that pressure over the bifurcation of the right common carotid could reproduce this vertigo and the unconsciousness. It also produced marked slowing of the pulse which did not follow after the administration of atropine. The sensitivity of the bifurcation could also be abolished when novocain was injected into the area. Operation was performed on March 15, 1938. The patient was discharged improved, April 7, 1938.

*Subsequent Course.*—On July 5, 1939, one year and three months following operation, the patient reported having "fainted" once. His blood pressure was 190/100, and he complained of dyspnea on exertion, headache, and palpitation. He had no pulse deficit. Other than complaints referable to his cardiac condition, the patient was well.

*Comment.*—The possibility of relationship between disturbances in the carotid sinus reflex and hyperthyroidism is suggested by this case. Heymans<sup>3</sup> pointed out the close anatomic relations between the base of the internal carotid artery and the origin of the superior thyroid artery in some subjects. The operative manipulation during ligation of the superior thyroid artery frequently will excite the reflex.

*CASE 2.*—V. C., white, male, Italian, aged 60 years, was admitted to the hospital in January, 1933, and in May, 1936, for brief periods, at which times his illness was diagnosed as acute and chronic paranasal sinusitis. He complained of attacks of dizziness and faintness. These were attributed to the sinus infection which was demonstrated roentgenologically. In December, 1936, he was readmitted, complaining of periodic attacks of headache, dizziness, vomiting, and occasionally diarrhea. There was no evidence of sinus disease at this time. Electrocardiographic tracings confirmed a diagnosis of auricular fibrillation. There was no cardiac enlargement. He remained in the hospital for sixteen days with no recurrence of the dizziness.

His last admission to the hospital was on Jan. 30, 1938; complaints were the same, the attacks being described as lasting about one hour. He was still fibrillating. At this time, it was discovered that pressure over the left carotid sinus produced marked dizziness, syncope, convulsive movements on the right side, and cessation of radial pulse. Pressure on the right carotid sinus caused slowing of the pulse, slight dizziness, but no unconsciousness. Electrocardiographic tracings taken while pressure was being applied showed a period of asystole lasting three seconds. The

body is only slightly stimulated by  $\text{CO}_2$  increases, but is highly sensitive to oxygen tension. In the absence of  $\text{CO}_2$  in the blood the carotid body becomes the controlling factor in respiration. This fact is of obvious clinical importance to both the anesthetist and the surgeon.

Blakemore, Humphreys, and King<sup>5</sup> created experimental carotid-jugular fistulas in dogs and demonstrated the effect of shunting of carotid blood away from the sinus. The reflex vasoconstriction, produced by the lack of endovascular tension beyond the fistula, increased the blood flow from artery to vein in a vicious manner. They rightfully concluded that the therapeutic creation of such a fistula is inadvisable. Their findings should be borne in mind in cases of traumatic arterio-venous aneurysms of the neck.

#### SUMMARY AND CONCLUSION

1. The procedures employed in the diagnosis, preoperative care, anesthetic management, and operation are described.
2. Mention is made of the clinical application of knowledge of this reflex area.
3. Five cases are cited briefly.
4. The symptoms of hyperactive carotid sinus reflex may be relieved by surgical denervation of the sinus.

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*Operation.*—On Nov. 15, 1938, a denervation of the carotid sinus on the right side was performed. Manipulation at the bifurcation of the common carotid caused long periods of asystole. After the nerve was cut, the pulse resumed a rate of 92. For six days following operation the patient complained of thickness of the tongue and flushing of the right side of the face. The right pupil was dilated. These symptoms gradually subsided and had disappeared at the time of discharge, Nov. 23, 1938.

*CASE 5.*—H. S., white, male, aged 45 years, was well until April, 1937, when he had an attack of dizziness which came on suddenly. He shook his head and after resting a few moments it cleared. These attacks have recurred about once a month, and during the last four weeks he has had five attacks of a severe nature associated with unconsciousness.

*Past History.*—The patient had had an initial attack of precordial pain followed by marked dyspnea and faintness in December, 1937. For this he was treated in the hospital for four months. On discharge he was taking digitalis, feeling well but still dyspneic on effort. He had had similar attacks for which he was hospitalized in July, 1938, and in October, 1938. Recently, he has had eight or nine attacks of nocturnal dyspnea. At the time of this admission, June 5, 1939, it was discovered that pressure on the right carotid sinus produced the same dizziness, vertigo, and unconsciousness of which the patient complained. The diagnosis made at this time was arteriosclerotic heart disease with coronary sclerosis and myocardial fibrosis. He had regular sinus rhythm and signs of heart failure were induced by moderate exertion. Electrocardiographic tracings taken during pressure over the right carotid sinus showed depression of the sinus node to a rate of 45 per minute with ventricular escapes. Pressure over the left sinus produced only slight slowing of the auricular and ventricular rates. Diagnostic blocking of the carotid sinus nerve with novocain was not done on this patient because of a sensitivity to the drug.

Operation was performed on June 28, 1939. The right carotid sinus was denervated. The blood pressure, which had fallen during early operative manipulation, rose when the nerve to the sinus was cut. The patient recovered promptly. During the postoperative period, pressure over the right sinus had no effect. He was discharged after seven days, improved.

The experience gained in the treatment of disturbances of the carotid sinus reflex has been of value in interpreting untoward symptoms occurring during operative procedures in the region of the bifurcation of the common carotid artery. Rovenstine and Cullen<sup>2</sup> have indicated the reflex may be an explanation for the sudden deaths which occasionally follow incision and drainage of neck infections. During operative manipulation in the region of the sinus the sudden occurrence of bradycardia, hypotension, pallor, and at times respiratory depression suggests stimulation of the reflex. Clamps, retractors, and packs which have been placed in the vicinity should be removed. Infiltration of the area between the internal and external carotid arteries with 5 c.c. of a 2 per cent solution of procaine will immediately abolish the reflex and restore the circulatory and respiratory functions. Indeed, this may be a lifesaving measure.

The role of the carotid body in the control of respiration has been indicated by Heymans<sup>3</sup> and demonstrated experimentally by Schmidt.<sup>4</sup> The latter showed that the respiratory center is sensitive to changes in the carbon dioxide tension of the blood but not to oxygen lack. The

body is only slightly stimulated by  $\text{CO}_2$  increases, but is highly sensitive to oxygen tension. In the absence of  $\text{CO}_2$  in the blood the carotid body becomes the controlling factor in respiration. This fact is of obvious clinical importance to both the anesthetist and the surgeon.

Blakemore, Humphreys, and King<sup>5</sup> created experimental carotid-jugular fistulas in dogs and demonstrated the effect of shunting of carotid blood away from the sinns. The reflex vasoconstriction, produced by the lack of endovascular tension beyond the fistula, increased the blood flow from artery to vein in a vicious manner. They rightfully concluded that the therapeutic creation of such a fistula is inadvisable. Their findings should be borne in mind in cases of traumatic arterio-venous aneurysms of the neck.

#### SUMMARY AND CONCLUSION

1. The procedures employed in the diagnosis, preoperative care, anesthetic management, and operation are described.
2. Mention is made of the clinical application of knowledge of this reflex area.
3. Five cases are cited briefly.
4. The symptoms of hyperactive carotid sinus reflex may be relieved by surgical denervation of the sinns.

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seem to be very radical treatment we do not doubt, and for that reason we wish to state that *we are not advising surgery as the primary treatment in cerebral hemorrhage, for no case has been operated upon unless there existed definite evidence of increasing intracranial pressure.*

Bagley<sup>7</sup> has advocated the surgical treatment of a certain group of cases of intracerebral hemorrhage, and he emphasizes the fact that, because of the poor general condition of these patients, the simplest procedure which will afford relief should be employed. In Case 1 all that was necessary was the aspiration of the old blood through a perforator opening, but in the other cases it was necessary to reflect an osteoplastic flap.

CASE 1.—A. C., a 46-year-old merchant, a known diabetic and hypertensive, was admitted to the Jewish Hospital on Nov. 24, 1938. Three days before admission, while driving his car, he suddenly developed a severe headache, dizziness, and nausea. He managed to stop the car, and a physician was summoned and gave him a hypodermic for relief. He was brought to the home of a relative, where he remained in bed for two days, but the headache continued to be so violent that he was sent into the hospital. When he entered, his blood pressure was 190/100, and there was some stiffness of his neck. The rest of the examination was without positive findings. One of us (L. T. F.) saw him on Nov. 26, 1938. At that time there was blurring of the nasal borders of both disks, stiff neck, bilateral Kernig, and blood pressure of 200/110. A diagnosis of spontaneous subarachnoid hemorrhage was made and lumbar puncture was done. The fluid was bloody and contained many crenated red cells, and when centrifugalized the supernatant fluid was yellow. Following the spinal puncture his headache was greatly relieved.

Spinal punctures were done daily, and on Nov. 28, 1938, the spinal pressure was 260 mm. of H<sub>2</sub>O, but the fundi had not changed. He continued to feel well, and from Dec. 4 to Dec. 14 he was not seen by us. On Dec. 14 it was discovered that in spite of total absence of headache he had developed a complete left homonymous hemianopsia and terrific choked disks with many hemorrhages and patches of exudate. Ventriculogram was done that afternoon. When the needle was inserted in the right parieto-occipital region, at 2 cm. under the surface, a large collection of old chocolate-colored blood was encountered and evacuated. The direction of the needle was then changed; air was injected into the ventricles, and, when x-ray films were made, the cavity could be seen, filled with air and connected with the ventricle. Since there was no ventricular displacement, no further surgery was done.

His postoperative course was smooth, and he was discharged on Dec. 20, 1938. The choked disks and the homonymous hemianopsia had entirely cleared up when last seen on March 9, 1939. Since that time, he has had no further trouble and is able to carry on his work.

In spite of the fact that symptomatically this patient improved after spinal punctures, his choked disks progressed to an alarming degree. Finally the stage was reached where permanent visual damage was feared, and the prompt subsidence of the choked disks and the homonymous hemianopsia after the removal of the hemorrhage was most gratifying.

# SPONTANEOUS CEREBRAL HEMORRHAGE

## THE SURGICAL TREATMENT OF SELECTED CASES

LEONARD T. FURLOW, M.D., ARCHIE D. CARR, M.D., AND  
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THAT certain cases of spontaneous cerebral hemorrhage may be treated by surgical means is not a new idea. According to Penfield,<sup>1</sup> Wernicke many years ago suggested that trepanation might be of benefit in "ingravescent apoplexy." Cushing,<sup>2</sup> in 1903 not only repeated the suggestion but actually carried it out in two cases, though in neither instance was a fatal outcome averted. Russel and Sargent<sup>3</sup> in 1907 reported the evacuation of a subcortical clot, but both to the authors and to those who discussed the case it seemed questionable if the operation was of benefit since the patient had a residual hemiplegia and an aphasia from the left-sided lesion. Penfield reported 2 cases operated upon with recovery and Craig and Adson<sup>4</sup> have encountered 9 cases, 6 of which were apparently truly "spontaneous" while two were probably traumatic in origin.

Merritt<sup>5</sup> has divided vascular lesions in the brain into four groups: (1) primary subarachnoid hemorrhage, (2) cerebral embolus, (3) cerebral thrombosis, and (4) cerebral hemorrhage. As a part of his discussion of the latter group he says: "In rare instances a cerebral hemorrhage may become encapsulated and present the symptom complex of a tumor. Such hemorrhages have been removed successfully in several instances but this mode of therapy is still in the experimental stage and is adapted to only a very small percentage of cases of cerebral hemorrhage."

It seems quite certain in the light of present knowledge that surgery should play no part in the treatment of primary subarachnoid hemorrhage, cerebral embolus, or cerebral thrombosis. Cadwalader,<sup>6</sup> however, in his study of apoplexy showed two things which are of great importance in a consideration of the subject from a surgical viewpoint: Most cerebral hemorrhages are large (of 72 specimens examined by him only 4 measured less than 4 cm. in the broadest diameter), and a relatively small percentage of cases are rapidly fatal.

With these facts in mind we have in the past fifteen months resorted to surgery in 5 cases of spontaneous cerebral hemorrhage, and it is our feeling that the results fully justify this report. That, to some, this may

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In Case 2 marked ventricular deformity after the aspiration of old blood was interpreted as evidence that simple aspiration was not sufficient, and, since the patient's condition was good, more radical measures were employed.



FIG. 1.—Case 2.

CASE 2.—R. W., female, aged 19 years, was admitted to Barnes Hospital on Feb. 20, 1939, in a stuporous state, having been ill about twenty-four hours. The evening before admission she suddenly complained of a severe headache, became nauseated, and a short time later said her left side felt "weak and queer." Headache and nausea persisted and during the following twenty-four hours she became more stuporous. She was seen by one of us (A. D. C.) at her college, about eighteen hours after onset, and the positive findings on neurologic examination were: hyperactive deep reflexes on the left side, increased tonus of muscles of left arm, defective position sense left upper and lower extremities, and complete left astereognosis.

Immediate hospitalization was advised, and at the time of admission little change was noted except that she had a central type of facial on the left and a left hemianopsia which was practically complete.

Her general physical examination was devoid of significant findings; blood pressure was normal, and all laboratory studies were within normal limits.



Fig. 2.—Case 2.

On Feb. 22, 1939, lumbar puncture was done. The initial pressure was 330 mm.  $H_2O$ ; fluid was clear; cell count, 8; and Ayala index, 3.5, suggesting an expanding lesion. The Wassermann reaction was negative on both blood and spinal fluid.

The next morning she was drowsy, nauseated, and complained of headache; the other signs were unchanged, and her pulse rate was beginning to become slow. Four days later the following note was made: "For three days patient has felt better, but her pulse has been becoming steadily slower. This morning she has headache and looks worse. There is some temporary improvement since having intravenous sucrose

but still her pulse is only 50, and has been between 48-56 for 18-20 hours. Fundi show no swelling but the slow pulse means an increasing intracranial pressure. The left-sided weakness, awkwardness, and astereognosis persist, but, because of the sudden onset, a vascular lesion is suspected. Ventriculogram is to be done."

On Feb. 27, 1939, when the needle was inserted for ventriculography on the right side, a few cubic centimeters of old brownish blood were evacuated. The needle was then put into the left ventricle, air injected, and films showed a marked ventricular shift to the left side with a downward and forward displacement of the right posterior horn and posterior part of the ventricular body (Figs. 1, 2, and 3). A right parieto-occipital craniotomy was done immediately, and in the parietal lobe an incision was made through a broadened convolution, and an old, firm, well-organized clot was removed. Sections of the cavity were removed for histologic study, but no tumor was found. There was very little fresh bleeding after the removal of the clot.



Fig. 3.—Case 2. The ventricles are displaced to the left side, and the posterior horn and posterior part of the body of the right ventricle are pushed down and forward.

Her postoperative course was very satisfactory, and within a few days the left-sided weakness, astereognosis, and loss of position sense cleared up. The left homonymous hemianopsia disappeared completely, and when last seen on March 1, 1940, she had absolutely no symptoms and was carrying on her work at the state university.

The etiology of the hemorrhage in this case has never been determined. Certainly a small miliary aneurysm is the condition we would consider most likely, but no such lesion could be seen at operation. Whatever

the underlying cause, however, the excellent result obtained by surgery is argument enough that in certain instances the operative treatment of intracerebral hemorrhage has passed the "experimental stage."

In Case 3 the surgical indications were perhaps less well defined for the etiologic factor was known to be a well-developed hypertension, and the lesion was on the left side. However, the lack of improvement after what seemed to us an adequate period of conservative therapy was, we felt, justification for more radical measures.

CASE 3.—A. L., a 50-year-old widow, who designed and made women's clothing, was admitted to Barnes Hospital on July 31, 1939, in an aphasic state. She was apparently well until that morning, when, shortly after arising, she complained of a severe occipital headache, was nauseated, and vomited. Shortly after this she had two generalized convulsions and upon regaining consciousness was markedly confused and aphasic. She was unable to name objects, could not read, and when asked what year it was said "Wednesday" and gave her age as fourteen.

Physical examination showed a blood pressure of 180/104. Pulse rate was 84; heart, slightly enlarged. Pupils were equal, fundi normal, and there was a right facial weakness. Patient moved all extremities freely, but there was a bilateral Babinski. The impression was that she had had a spontaneous cerebral hemorrhage on the left side.

The following day her speech was markedly confused, but she obeyed simple commands. She could not name a fountain pen, bag, etc., but said the match was a "scratch." The right facial paresis was unchanged, the fundi were normal, and the bilateral Babinski persisted. X-rays of her skull had been made, and were not abnormal. Urine showed no albumin or casts. R.B.C. and Hb. were normal and W.B.C. was 17,600 with a normal differential.

The next day her speech was somewhat better in that she occasionally used a phrase correctly, but she was drowsy and at times very difficult to arouse. A spinal puncture done that day showed an initial pressure of 370 mm. H<sub>2</sub>O with 40,000 red cells mostly crenated. The fluid was pinkish throughout, and the Ayala index of 4 was suggestive of an expanding lesion.

The following morning she was much worse. Her temperature rose to 39.4° C.; she was unconscious and had a right hemiplegia. There was some stiffness of the neck, and the spinal fluid showed approximately the same cell count. She was given hypertonic sucrose; a nasal tube was inserted for feedings; and her condition remained practically unchanged until Aug. 14, 1939, when the following note was made: "This patient has shown no improvement for eleven days. The veins in both fundi are full and tortuous, and she is stuporous all the time. The right hemiplegia persists, and because she may well have a large subcortical clot ventriculogram is to be done. If the films show a space-occupying lesion craniotomy will be done immediately."

On Aug. 15, 1939, a ventriculogram showed both lateral ventricles and the third ventricle displaced to the right side (Fig. 4) with no air in the left temporal horn; whereas, the right was well filled. Immediate left cerebral craniotomy was done, and there was considerable greenish brown discoloration of the area around the Sylvian fissure. The first temporal convolution was broadened and a needle introduced through this convolution evacuated 15 to 20 c.c. of old brownish blood. Following this the cortex herniated rather rapidly and it was necessary to incise this convolution and with suction remove a large fairly firm clot. Tissue from the wall

of the cavity was taken for section to be sure we were not dealing with a tumor, and a decompression was done (the sections did not show tumor).

Her postoperative course was satisfactory, and she was discharged on Aug. 28, 1939. At that time she could only say a few words and her hemiparesis was almost complete, although she was beginning to move the leg.

She was last seen in March, 1940. At that time she was walking alone, and was able to use the arm and hand well enough for sewing. The spontaneous speech was quite good, although when she became excited she had difficulty in naming objects. Although her blood pressure varies between 190/110 and 220/140, she was leading a fairly normal life.

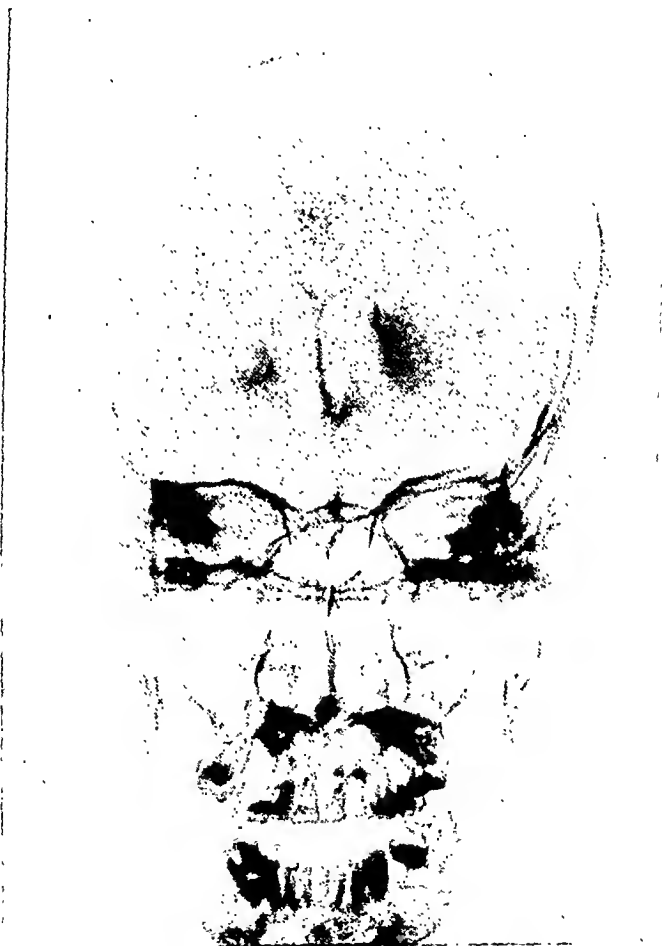


Fig. 4.—Case 3. Ventricles pushed over to right side.

It is, of course, impossible to state definitely that there is more improvement as a result of the surgery than there would have been had this patient been continued on "conservative" treatment. In our opinion surgery was indicated because the patient was slowly going downhill, and we believe that it was both justified and beneficial. The clot was

so large that it seems unlikely that complete absorption ever would have taken place, and, while it was unfortunate that the first temporal convolution on the left side had to be incised, no other course was open.

Case 4 had a fatal outcome, probably for two chief reasons. In the first place, surgery was too long delayed; second, the development and progression of an obstructive hydrocephalus were unrecognized.

CASE 4.—O. T. H., a 59-year-old housewife, eight days before entry had developed a severe headache of sudden onset accompanied by nausea, vomiting, and prostration. She was found to have a fairly well-developed generalized arteriosclerosis with moderate hypertension, the blood pressure averaging 185 systolic and 90 diastolic. The neurologic findings were entirely normal except for some stiffness of her neck. All laboratory studies were within the range of normal, and x-rays of the skull showed nothing pathologic. A spinal puncture done on the third day of her hospital stay showed xanthochromic fluid under a pressure of 140 mm. of  $H_2O$ . After the removal of fluid, her headache subsided completely and she was discharged on Aug. 5, 1939, with the diagnosis of spontaneous subarachnoid hemorrhage, hypertension, and arteriosclerosis.

On Aug. 14, 1939, she was readmitted to Barnes Hospital. Two days before there had been a sudden recurrence of the severe headache with nausea, vomiting, and prostration. There was some stiffness of her neck, a questionable Babinski on the right side, and the same degree of hypertension. A lumbar puncture done shortly after admission again showed xanthochromic fluid, but the headache was not influenced by the puncture. On Aug. 17, 1939, she was seen in consultation by one of us (L. T. F.) and the following note made: "The only positive neurological finding is a Babinski on the right side. There is no question but that this patient has had an intracranial hemorrhage and it is my feeling that, at least for the present, she should be conservatively managed. However, it is possible that she will, later on, have to have surgery for the removal of a clot. Careful spinal punctures with pressure readings should be done."

There was no appreciable change in her condition until Aug. 24, 1939, when she suddenly complained of severe headache, was nauseated and vomited, and then became unconscious and had a series of generalized tonic convulsions with opisthotonos and extensor rigidity of all extremities. Intravenous sucrose was given, and a spinal puncture done. The fluid was grossly uniformly bloody, and there was no appreciable change in her condition after the removal of fluid. Her blood pressure continued rather markedly elevated and a venesection was done on Aug. 29. She remained comatose and for the most part in a state of extensor rigidity. On Aug. 30 she had a period of respiratory failure, but after about ten minutes of artificial respiration she began to breathe spontaneously. These episodes of respiratory difficulty continued to occur at intervals until about Sept. 15.

On Sept. 1 she was transferred to the neurosurgical service. Nasal tube feedings were begun, and spinal punctures done at intervals continued to show gross blood. Punctures were omitted after Sept. 12, and she remained totally comatose and frequently in a state of tonic spasm. On Oct. 2 the following note was made (L. T. F.): "For over six weeks this patient has been comatose with no response to any stimulus. There are periods of rigidity, and her blood pressure, although constantly elevated, is extremely variable. For the first time today she shows some papilledema, and in view of this evidence of increased pressure I think we should do a ventriculogram to see if there might be a removable clot."

It was ten days before the patient's family decided that surgery should be undertaken and on Oct. 12 ventriculogram was done. Fifty-five cubic centimeters of slightly yellowish fluid which contained a few shreds of organized clot were removed and an equal amount of air injected. The films (Fig. 5) showed a symmetrical dilatation of both lateral ventricles, but in the right frontal lobe, anterior and slightly beneath the anterior horn, was a cavity connected with the ventricle. It was partially filled with air. The third ventricle was slightly displaced to the left side, so it was concluded that this cavity was the site of a hemorrhage which had broken through into the ventricle.

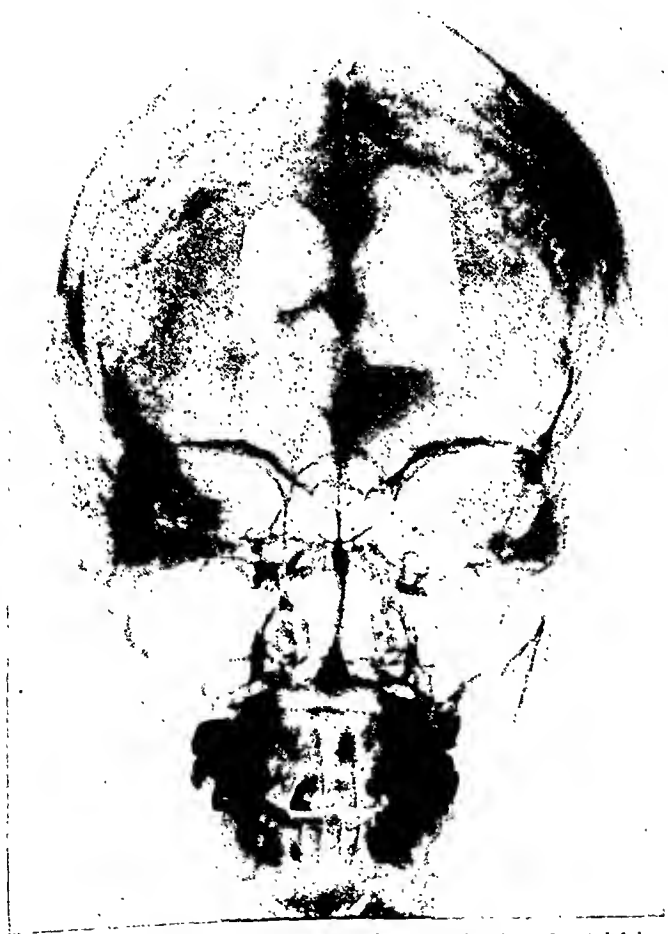


Fig. 5.—Case 4. Dilated ventricles with cavity in right frontal lobe.

A right frontal craniotomy was done immediately, using only local anesthesia. The prefrontal area was markedly discolored as a result of old blood pigment, and about 5 c.c. of old blood was removed with a needle. A circular area of cortex was then excised, and at a depth of 4 cm. the cavity which contained old, well-organized clot was exposed. The clot was removed, and it was seen that the posterior part of the cavity communicated with the ventricle. The source of the bleeding could not be determined, and there was no fresh bleeding after the clot was removed.



In this case, even at autopsy, it was impossible to determine the source of the bleeding, but there was no evidence of an aneurysm.

Case 5 occurred, as did the second, in a young individual with no evidence of hypertension.

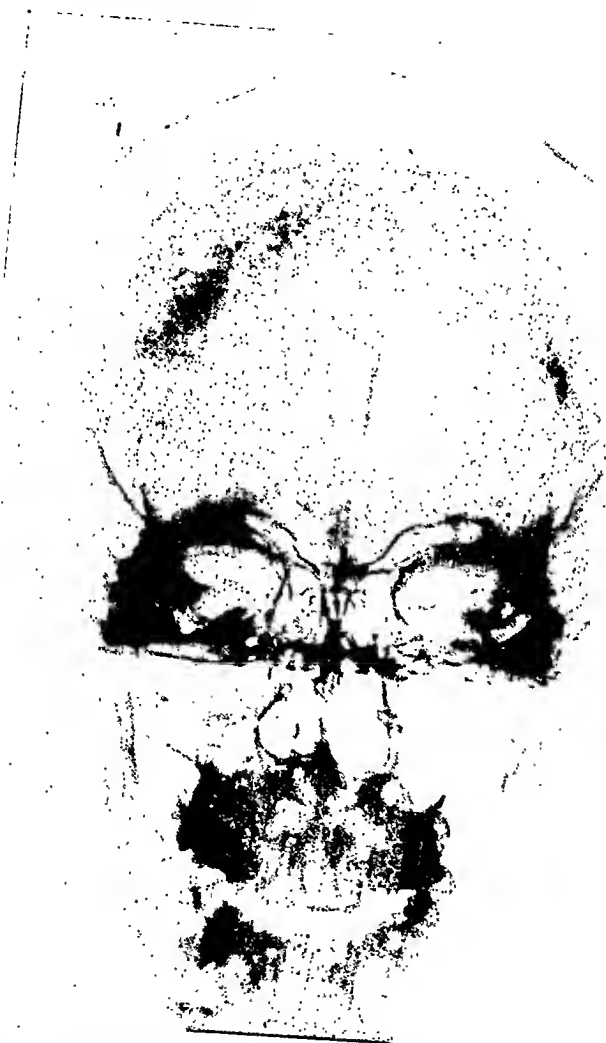


Fig. 7.—Case 5. Showing the slight displacement of the ventricular system to the left side after the aspiration of old blood.

CASE 5.—S. M. D., a 30-year-old white man, was admitted to Barnes Hospital Jan. 30, 1940. His family history and past history were unimportant. The present illness had begun three weeks before with sudden severe headache for which he had sinus treatments. The headache continued, and one week later he developed a progressive weakness of the left arm and leg with awkwardness, clumsiness, and dragging of the leg in walking. Three days before admission he became dizzy and fell, striking his occiput, but was not unconscious. During the twenty-four hours before admission he became very drowsy and developed a slow pulse.

Neurologic examination on admission showed: (1) right pupil larger than left, (2) choking of both disks of slight degree with full tortuous vessels, (3) left hemiparesis involving face, arm, and leg, and (4) loss of position sense on the left side. The visual fields could not be checked because of his drowsiness.

The blood pressure was 136/78; all laboratory studies were within normal limits, and x-rays of the skull showed no abnormality.

The impression was that he had either a tumor or an abscess, and Dr. H. G. Schwartz did a ventriculogram and craniotomy on Jan. 31, 1940. The left ventricle was first injected and this ventricle and the third were found to be displaced to the left side. A needle was then inserted into the right side and about 6 c.c. of old, dark blood was evacuated, followed by a small amount of ventricle fluid. The films showed an irregular cavity connected with the ventricle, but, since the ventricles were still displaced (Fig. 7), a flap was reflected. Aspiration revealed old blood at a depth of about 6 cm., and through three different punctures a total of 50 c.c. was removed. Since this was a rather deeply situated hemorrhage, the cortex was not incised, it being wisely decided to see if aspiration was not sufficient.

His postoperative course was entirely uneventful, and by the time of his discharge on Feb. 14, 1940, all of his symptoms had cleared up, but the deep reflexes on the left side were slightly more active than on the right. He is now perfectly well.

Unquestionably it was wise in this instance not to incise the cortex, but it was essential that the brain be exposed by an osteoplastic flap so that the relief of pressure could be judged. The removal of 50 c.c. of old blood was enough to relieve the increased intracranial pressure.

#### SUMMARY

Five cases of truly spontaneous cerebral hemorrhage treated by surgery are reported. All of these patients have been seen in the past fifteen months.

Three of the individuals were hypertensive; two had normal blood pressures. Four patients recovered. Three had been entirely relieved of all symptoms due to the hemorrhage, while one still has some residual hemiparesis and slight aphasia disturbance.

There was one death due to obstructive hydrocephalus which developed as a result of occlusion of the foramina of Magendie and Luschka.

Ventriculography may be used as an index in determining the extent of the surgical procedure. If, after aspiration of the old blood, the ventricles occupy a normal position, no further surgery is indicated; but, if there is still ventricular displacement, a small flap should be reflected and the clot removed.

It is wise to take tissue for section from the wall of the hemorrhagic cavity to ascertain if the hemorrhage has occurred into a tumor.

#### CONCLUSIONS

1. While it may seem radical to some, it is our feeling that in well-selected cases surgery may be of definite value in the treatment of spontaneous cerebral hemorrhage.

2. In our opinion, however, surgery should be undertaken only (a) when conservative measures have failed to produce improvement; (b) when there is some definite evidence of increased intracranial pressure, such as choked disks, slow pulse, or high spinal pressure; or if (c) the presence of arteriosclerosis and hypertension does not constitute a contraindication to operation. It is true that other hemorrhages may occur, but, if so, perhaps not for several years.

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## ACUTE TROCHANTERIC BURSITIS WITH CALCIFICATION

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THE clinical picture of acute trochanteric bursitis with calcification is not widely known. Consequently, errors in diagnosis are common. In the literature extremely few observations are recorded, while more attention has been given to chronic trochanteric calcifications.

In 1927 Steger, in Stegemann's clinic, reported five cases in which he localized the calcium deposit as either in the bursa, the tendon insertion adjacent, or the para-articular tissues in general. He attributed the clinical symptoms to the bursitis caused by mechanical irritation.

Stegemann, in 1923 and later in 1930, reported similar cases in which calcification was noted and disappeared after diathermy. He drew the direct comparison with the shoulder as to calcification in the bursa and tendon insertion. He stressed the spontaneous onset of pain and emphasized the possibility of confusion with periosteal trochanteric injuries and infections.

Rouillard and Gloppe, in 1928, reported a case entitled "Calcification of Serous Bursae With Acute Painful Attacks Like Rheumatism." Their patient had disabling pain in the trochanteric region, fever and chills accompanied by roentgen evidence of calcification. There was complete recovery in one month with salicylate medication.

Nilsonne, in 1930, and Lecoq, as the first American author in 1931, described almost identical cases. Both had a history of preceding injury, followed after an interval of a year by chronic increasing hip disability; both showed a large calcification lateral to the greater trochanter. At operation both had the calcification in the gluteus medius tendon and muscle and marked inflammation of the adjacent bursa. Nilsonne remarked that the symptoms were due to the bursitis and not the calcification as Waldenstrom had demonstrated for the shoulder. Rubarov, in 1936, reported a similar case in which operation was not performed and symptoms subsided spontaneously. Goldenberg and Leventhal, in 1936, mentioned that two bursae were constantly present about the greater trochanter: (1) between the gluteus maximus and tendon of the gluteus medius, and (2) between the latter tendon and the bone. They classified the various types of supratrochanteric calcification as occurring (1) in the tendon of the gluteus medius, (2) in the bursa between this tendon and the greater trochanter, and (3) away from the trochanter on the undersurface of the gluteus medius muscle. They used routine hip x-rays and clinic records to obtain their data and described several chronic cases.

Hitchcock described para-articular calcifications with acute symptoms in various localities, including the hand, quadriceps, elbow, ankle, finger, and shoulder, as well as in one case in the supratrochanteric region. This patient had but a few weeks' history and was cured in several months by diathermy, although she returned to work in ten days. He stressed the traumatic etiology and ascribed the symptoms to "calcium gout" with fever, local pain, swelling, redness, and heat.

Finally, Sandstrom, in 1938, summarized the results of many years of study of these calcifications from the roentgenologic aspects. His larger series included cases of trochanteric bursal calcification. He discussed the analogy between shoulder, hip, and other regions as well and stressed its amenability to roentgen therapy.



Fig. 1.

*Presentation of Cases.*—Although the occurrence of these calcifications and their pathogenesis and location have been well described by the above authors, none has delineated clearly the picture of acute trochanteric bursitis with calcification which resembles so strikingly the much described picture of acute subdeltoid bursitis with calcification. In the past few years at the Mount Sinai Hospital we have observed seven cases. After attention had been drawn to the existence of this entity, the correct diagnosis was made in the last five cases before x-ray examination.

*Summary of Findings in Cases.*—There were three males and four females, their ages ranging from 42 to 58 years. Four patients had complained of pains in the affected hip region previous to the present illness. Two had calcific bursitis of the shoulder before or after the trochanteric involvement. One patient regarded exposure to cold as the cause of his ailment, while the others knew of no preceding cause.

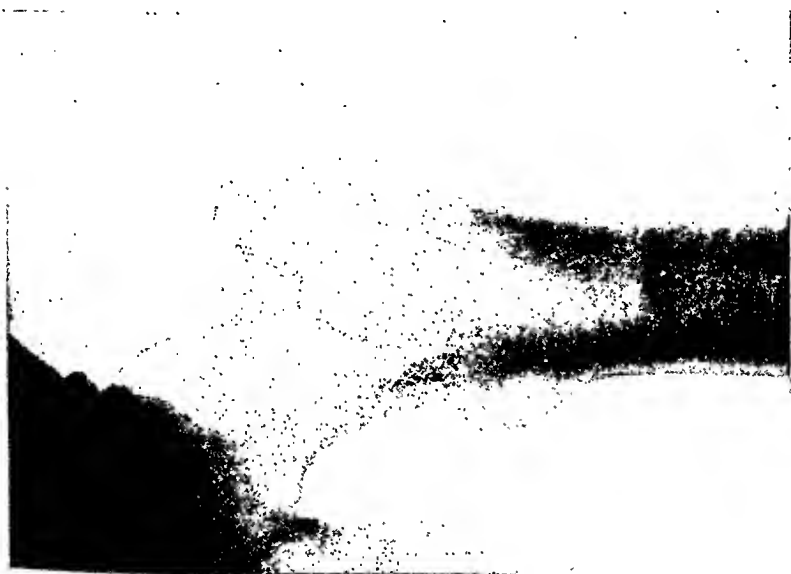


Fig. 2.



The presenting symptoms were remarkably constant; i.e., severe pain in the hip region with inability to walk about, with onset less than forty-eight hours before examination. The outstanding physical findings

were exquisite localized tenderness over the greater trochanter, severe pain on abduction and rotation of the affected hip, little or no pain on flexion, and no tenderness over the hip joint proper.

Five patients had a temperature elevation to about  $101^{\circ}$ . In the remaining two the temperature was not recorded.

X-ray examination showed calcifications in all cases but the density, configuration, and position of the shadows varied. In five cases the calcification was situated lateral to the upper part of the greater trochanter. In the other two cases it was above the tip of the greater trochanter.



FIG. 3.

The total course was limited to three days or less in six patients, and the other also recovered promptly. The treatment varied, consisting of bed rest, cold or hot applications, or local infiltration of the calcific area with novocain. In four cases, followed for nine months to over one year, there was no recurrence. Disappearance of the calcification was verified by x-ray in two cases after one month.

*Differential Diagnosis.*—In accordance with these findings, the diagnosis of this clear-cut condition should be relatively easy. This is important because any acute lesion of the hip region associated with fever and pain on motion arouses fear of a serious and prolonged illness. The

following conditions must be ruled out: (1) lesions of the hip joint proper and (2) lesions of the trochanteric region.

These lesions may be fractures, arthritis, osteomyelitis, traumatic periostitis, or even neoplasm, such as Ewing's tumor. Involvement of the hip joint can be eliminated by the location of pain and tenderness

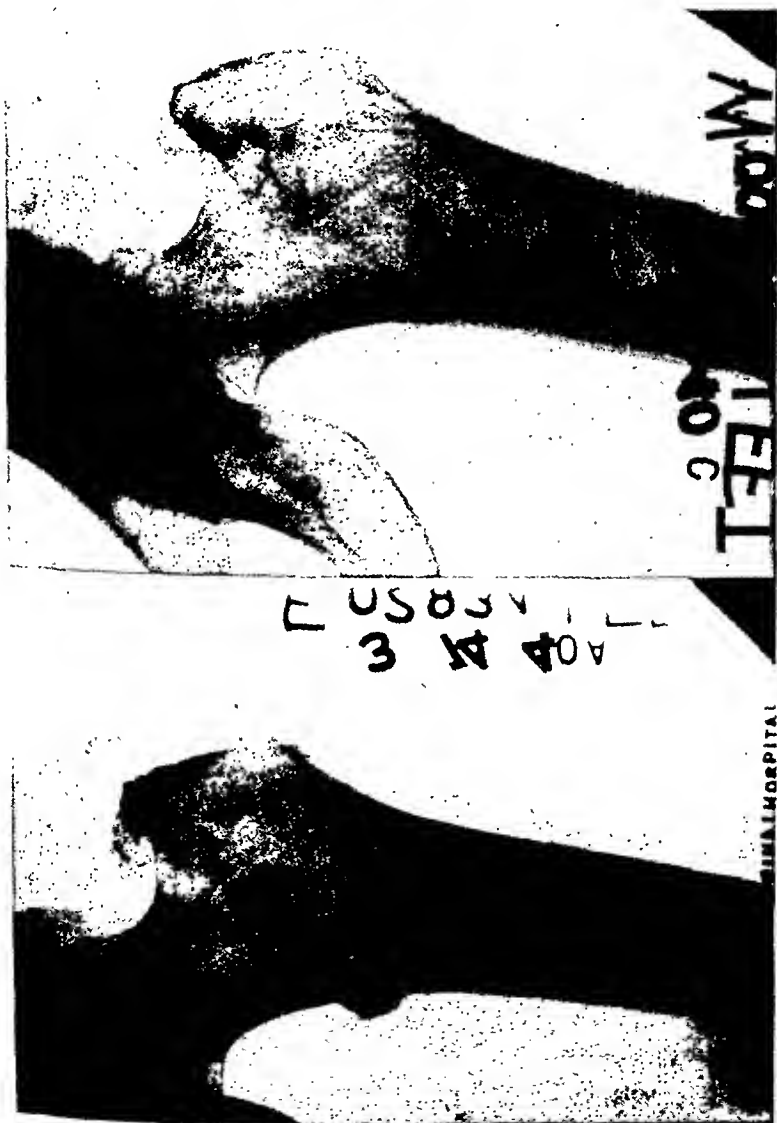


Fig. 4.

over the tip of the trochanter and the relative freedom of flexion and extension as compared to abduction, adduction, and rotation.

The x-ray evidence of a calcific deposit distinguishes this condition from the other trochanteric lesions. However, occasionally in the presence of a recent history of injury, calcific trochanteric bursitis may be

TABLE I

CASE	PREVIOUS HISTORY	PRESENTING SYMPTOMS	PHYSICAL FINDINGS	X-RAY FINDINGS	TREATMENT	RESULT
1. White, male, painter, aged 55 years (1936)	Severe pain in left hip region ten years before; relieved by injection, type unknown	Severe pain in left hip region of one week's duration; inability to walk	Marked tenderness over left greater trochanter; motion of left hip joint guarded but not limited Temperature, 101° F.	Calcific deposit above the left greater trochanter	Bed rest	Symptom free in two days; no follow-up
2. White, female, housewife, aged 52 years (1938)	Mild pain in right hip region one year ago; relieved by diathermy	Severe pain in right hip region of twelve hours' duration; inability to walk	Marked tenderness over right greater trochanter; pain on motion of right hip, but no limitation Temperature, 101° F.	Calcific shadow lateral to right greater trochanter	Bed rest, local heat for two weeks, followed by diathermy	Symptom free in two weeks; no recurrence in one year
3. White, female, housekeeper, aged 49 years (1938)	Right subdeltoid bursitis with calcification two years before; pain in right hip one-half year ago; subacute spontaneous	Severe pain in right hip region of forty-eight hours' duration; inability to walk	Marked tenderness over right greater trochanter; flexion of hip painless; abduction and rotation very painful Temperature, 101.4° F.	Fine calcific shadow lateral to tip of the right greater trochanter	Bed rest, ice application	Symptom free in three days; no recurrence in one year

4. White, male, read estate agent, aged 42 years (1938)	Slight stiffness in right hip one month ago	Severe pain in right hip region of twelve hours' duration; inability to walk	Marked tenderness over right greater trochanter; flexion of hip painless; abduction and rotation very painful Temperature, 101° F.	Moderate calcific deposit lateral to the right greater trochanter	Injection of 0.5 per cent novocain into tender area, followed by bed rest and ice application	Symptom free in three days (calcium deposit disappeared after four weeks on x-ray); no recurrence in one year
5. Puerto-Rican female, lunatic, dry worker, aged 42 years (1939)		Increasing pain in left hip region of one week's duration; inability to walk	Marked tenderness over left greater trochanter; flexion of hip painless; abduction and rotation very painful	Small calcific shadow above the left greater trochanter	Injection of 2 per cent novocain into tender area	Immediate relief; no follow-up; not hospitalized
6. Colored, male, laborer, aged 47 years (1949)		Severe pain in right hip region of twenty-four hours' duration; inability to walk	Marked tenderness over right greater trochanter; flexion of hip painless; abduction, adduction and rotation very painful	Large calcific deposit lateral to the right greater trochanter	Injection of 2 per cent novocain into tender area	Immediate relief; eight months follow-up; not hospitalized
7. White, female, housewife, aged 58 years (1940)	Dull pain left hip and thigh for six months; worse in lying on that side	Severe pain in left hip region with inability to walk 4 days ago	Marked localized tenderness over tip of greater trochanter; all movements of left hip restricted except flexion fairly free Temperature, 101° F.	Diffuse calcific deposit lateral to tip of greater trochanter	Injection of 1 per cent novocain; attempted aspiration; bed rest	Symptom free in two days; x-ray after one month shows calcific deposit almost gone

confused with avulsion fracture of the greater trochanter, as was done in a case reported by Milch.

#### DISCUSSION

The analogy between calcific subdeltoid bursitis and calcific trochanteric bursitis has been noted by several of the authors mentioned in the review of the literature. They dealt largely with the chronic forms. The analogy between the acute cases is just as obvious. The anatomical site of the calcification in a tendon adjacent to a bursa, which in turn is near the large joint at the proximal end of the limb, the history of previous low grade symptoms in the same region terminating in an acute disabling exacerbation, the presumably similar pathogenesis, and the response to therapy, all confirm the analogy.

The theory of pathogenesis of this lesion, as developed for the shoulder, can be applied to the hip. A preceding injury or degeneration, clinically with little or no symptoms, occurs in the gluteus medius tendon, which is an avascular structure. Healing occurs by calcification instead of fibrous scar. This gradually enlarges until it erodes into an adjacent bursa, either the large trochanteric bursa externally or the smaller one between the gluteus medius tendon and the trochanter tip, internally. The chemical bursitis gives rise to the acute onset of symptoms.

Clinical healing of the condition is associated with production of hyperemia. Anything causing increased vascularity causes absorption of the calcific deposit and cure. The very inflammation of the bursa with its hyperemia accounts for the frequency of spontaneous cure. This explains why such varied therapeutic methods as diathermy, static brush discharge, x-ray therapy, local application of heat and cold, infiltration with novocain, and aspiration of calcific material have been advanced as the best forms of treatment. They each constitute a method of increasing local hyperemia, and all produce the same general results with varying rapidity.

In contrast to the shoulder, the hip symptoms appeared to subside much more rapidly and no recurrences have been noted.

#### SUMMARY AND CONCLUSIONS

1. The literature on trochanteric calcifications has been reviewed.
2. Acute trochanteric bursitis, with calcification, is a well-defined clinical entity as exemplified by seven case reports.
3. The differential diagnosis has been discussed.
4. The analogy with acute calcific subdeltoid bursitis is stressed.
5. The favorable prognosis with any form of therapy which induces hyperemia locally has been emphasized. Infiltration with novocain and multiple punctures of the calcific area appear most efficacious.

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# THE ROLE OF ESTROGENIC SUBSTANCES IN THE PRODUCTION OF MALIGNANT MAMMARY LESIONS

WITH REPORT OF CASE OF ADENOCARCINOMA OF THE BREAST, POSSIBLY INDUCED BY STRENUOUS ESTROGEN THERAPY

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EVIDENCE increasingly tends to accentuate reported experimental work on the carcinogenic activity of the estrogens as regards their role in the production of malignant mammary lesions. LaCassagne,<sup>1</sup> in his earlier experiments, demonstrated that the long-continued administration of these substances to mice of a strain normally capable of developing spontaneous mammary adenocarcinoma in females only led to the development of such malignancy within the males. This work was very promptly confirmed by Burrows<sup>2</sup> and Bonser.<sup>3</sup> It has further been shown by Suntzeff, Burns, Moskop, and Loeb<sup>4</sup> that it is possible in mice to increase the incidence of mammary cancer by long-continued injections of estrogen; these authors state that the effects of the drug vary directly with the size of the dose administered and with the hereditary tendency of a given strain to develop cancer. The experiments of these authors indicate that the hormone plays a significant etiological role in the production of malignant mammary lesions, for, by increasing or decreasing the amount of hormone administered, the results were concordant; namely, the greater the amount of hormone allowed to act, the greater the effect produced. Heredity also played a most important part in the end results of their experimental work, for the more marked the hereditary responsiveness of the tissue, the greater the number of the tumors which developed and the earlier these lesions appeared. Many investigators have shown that the mammary glands of male mice are hereditarily, at least, as predisposed to the development of carcinoma as are the glands of female. Following the injection of identical amounts of estrogen in male and female mice, cancer develops as readily, or perhaps more readily, in the male than in the female. Gardner and his co-workers<sup>5</sup> state that mammary cancer seems to be of a sex-limited character in the mouse, depending on either "the feminizing effects of the female sex hormone and the induction of growth of the mammary glands to serve as a substratum for differentiation of growth of cancer or a specific agent stimulating unrestricted mammary growth." Emge<sup>6</sup> experimented on a strain of white mice entirely free from spontaneous carcinoma and injected these animals of different ages, over varying periods, with varying doses of theelin and theelin

in oil, but he was not able in this fashion to produce malignant changes in the mammary glands or in the genital tracts. Emge assumed that an hereditary immunity protected the breasts and genital tissues of the rat against excessive and uncontrollable proliferation, regardless of the receipt of massive doses of the estrogens, and he believes that the substance does not affect other species of mammalia in a precisely similar manner. Geschickter,<sup>7</sup> on the contrary, has been able to induce mammary cancer in approximately 100 per cent of normally nonsusceptible animals, males or females, castrate or noncastrate, that have lived through the required time limit of six months or more, provided they were given the proper dosage of estrogen. This author states that estrogenic mammary carcinoma in rats indicates that cancer results from the physiologic action of the endocrine substance used, rather than from a direct carcinogenic action dependent upon chemical irritations, and he holds that genetic factors are of minor importance. Geschickter's proof lies in the fact that the cancers produced in his experimental studies did not occur at the site at which the hormone was implanted or injected, but in a remote organ subject to hormonal physiologic control. Additional evidence is offered by the fact that the time required for the appearance of the cancer is inversely proportional to the physiologic intensity of the stimulus, the time required being reduced if a high daily dose is injected or if a more constant means of absorption is provided (such as implantation of pellets) or if compounds of greater estrogenic potency are administered, and by the further fact that synthetic estrogens of a different chemical nature (e.g., diethyl stilbestrol) but of similar physiologic action produce similar forms of mammary cancer. Influenced by his experimental work, as well as by his clinical observations, Geschickter advocates x-ray sterilization of young women possessed of hard, scirrhus types of cancer of a size of 5 cm. or more, believing that these individuals are favorably influenced by such therapy in that metastases, if they do appear, occur at a later date.

McBryde<sup>8</sup> has shown that estrogen applied to the skin of women is absorbed directly into the breast tissue and administered by this route is capable of producing a characteristic stimulation of mammary growth. Allen<sup>9</sup> offers a criticism of experiments dependent for their success on the administration of massive doses of estrogen to produce carcinoma, stating that the secretion of endogenous hormone from the animal's own glands could not possibly approximate the large doses employed experimentally for this purpose. However, Pfeiffer,<sup>9</sup> according to Allen, showed that in rodents there is a sexual difference in the secretion of gonadotropic hormone by the pituitary, the pituitary of the male being several times more potent than that of the female. Pfeiffer<sup>9</sup> successfully transplanted the testes to female mice the day after birth with successful vascularization and normal growth of the transplant resulting in mice of the same inbred strain. Secretion from the transplanted testes masculinizes the female pituitary in that it induces it to secrete gonadot-

tropic hormones at the same level as that of the male. Due to the increased gonadotropic hormone level, a hyperovarian endocrine condition resulted, as evidenced by the fact that the uterus and mammary glands of the animals showed atypical growth similar to those described as produced by long-continued estrogen stimulation. However, there was no comparison between the amount of ovarian secretion and that which had been used to produce carcinoma. That the liver plays an important role in detoxifying the estrogens is shown by the fact that experimental damage to the liver decreases the amounts of this substance that are necessarily given to produce cancer and such hepatic damage likewise shortens the time interval of appearance of mammary cancer. This fact, if the same holds true for human beings, would be worthy of clinical comment.

Hoffman<sup>10</sup> has studied the effect of large doses of estrogen on the histologic structure of the human breast. Tissues for examination were obtained while performing plastic operations on the breast, and the author reports the case of a woman in the reproductive age who had been given a total of 250,000 units of estrodiol benzoate. Breast tissue from this patient removed on the twenty-third day of the menstrual cycle showed an increase in the milk ducts and an increase in the alveolar tissue with extreme hyperemia and edema. Shortly after the experiments of LaCassagne and others, the Council on Pharmacy and Chemistry of the American Medical Association<sup>11</sup> warned of the possible deleterious effect from the clinical administration of the estrogenic substances and repeated warnings have appeared in the *Journal of the American Medical Association*<sup>12</sup> regarding the indiscriminate use of estrogen. In a recent article entitled "The Public Be Warned"<sup>13</sup> the authors again cautioned against the indiscriminate use of hormones, especially at the hands of laymen. It was repeated that the hormone in specific amounts possesses the potentiality of bringing about serious changes in the genital and reproductive organs of women and that such therapy may induce changes in the breast with the subsequent development of cancer, especially in women possessed of an hereditary tendency. McBryde,<sup>8</sup> as previously mentioned, has shown that these products can produce changes by local application alone.

The first reported case of adenocarcinoma of the breast presumably induced by strenuous estrogenic therapy was reported by Allaben and Owen.<sup>14</sup> The authors lacked positive proof that the lesion in their case was produced by estrogen, but the story tended to incriminate heavy and prolonged estrogen therapy which had been administered. It is of some significance that the patient whose record was reported had only a very slight hereditary tendency to cancer, there having been but a single instance of malignancy (and that not of the breast) in the family history. Auchincloss and Haagensen<sup>15</sup> have more recently reported a case in which cancer of the breast developed in a patient subjected to prolonged treatment with estrogen. These authors likewise were not

able to conclude positively that the estrodiol benzoate which the patient had received was the cause, or for that matter the contributing factor, in the production of the malignant mammary lesion that was present. It was felt, however, that such was possible if not indeed highly probable. Their conclusion that until more is known about the effects of the estrogen substances their use should be avoided in large or prolonged doses appears sound as does their warning to avoid such therapy if there is a history of carcinoma in the family. If these drugs are employed, careful initial and repeated examinations should be made of both breasts. Finally, in patients having chronic mastitis, carcinoma, or any form of breast neoplasm, either before or after surgical treatment or radiation, such therapy is unwise.

Anspach<sup>16</sup> has recently referred to a patient observed by him who developed a malignant mammary growth following long and ill-advised estrogen therapy.

We have recently observed an instance of adenocarcinoma of the breast, in which we feel that the estrogens given elsewhere over a prolonged space of time may have played a part in the production of the neoplasm referred to.

**CASE REPORT.**—The patient, a white female, 54 years of age, was admitted to the Vicksburg Clinic on April 12, 1940, presenting as her chief complaint the presence of a "lump in the right breast." In March, 1936, almost precisely four years previously, while taking a bath she noticed a lump in the upper quadrant of the right breast. The following day she consulted her family physician, who confirmed the presence of a mass. The breast was supported by adhesive strapping and theelin, 2,000 units, was advised and administered twice weekly. At the end of three weeks, the tumor in the breast had entirely disappeared. Nonetheless theelin injections were continued twice weekly for four additional months. The patient stated that, even after disappearance of the tumor, there was at times engorgement of the breast, but this symptom disappeared after theelin was discontinued.

The patient then developed menopausal symptoms, the periods becoming irregular and scant. No further injections of theelin were given for six months, then, because of persistence of these symptoms, administration of theelin was again commenced, the patient receiving twelve injections of 2,000 units each. The drug was then discontinued for one month and then again twelve injections were administered. No further difficulty with the breasts was experienced until August, 1939, at which time it was noticed that both organs were engorged and very tender. The blood pressure and metabolic levels were found to be below normal. The patient was then given 2 gr. of thyroid extract daily and in addition theelin injections of 2,000 units each were administered on alternate days for three weeks. The drug in this dosage was then given for three weeks. The drug in this dosage was then given twice weekly for four additional months. After the third week of such therapy the soreness subsided in the left breast, but a "lump" remained in the right breast, being situated in approximately the same area as noted three years previously. By December, 1939, the lump had subsided somewhat but was still palpable and tender.

By Christmas, 1939, the patient felt well and all medication was discontinued through the holidays. In January, 1940, she suffered a severe attack of influenza and in the latter part of February she had a sudden onset of acute inflammation

of the right breast. This process developed in twenty-four hours and had all the usual evidence of an acute inflammatory lesion, with radiation of pain to the right shoulder and axilla and shooting pains in the right hemithorax. Treatment was again instituted by her physician, the therapy consisting of the application of diathermy to the breast daily for ten days, then on alternate days, and finally each third day. Two thousand units of theelin were given on alternate days. The signs of the acute inflammatory process subsided somewhat, but the mass in the right breast grew larger and remained tender. Under the above regime, the patient showed unsatisfactory progress and on that account reported to the Clinic for treatment.

The past history was not remarkable. Neuritis, involving the right shoulder and arm, had been present two years previously, at which time eight teeth were extracted and relief was obtained. Roentgenograms of the chest and gastrointestinal tract, done elsewhere in 1938, were reported as negative.

The family history, so far as malignancy was concerned, was entirely negative.

The patient, a housewife, lived under excellent surroundings and circumstances and her personal and social histories were not remarkable.

The menstrual periods were established at 14 years of age. The menopause occurred at 52 years of age (1938). The patient was married and had one child living and well. One child born prematurely had been dead at birth. The marital and puerperal histories were otherwise not remarkable.

Physical examination revealed a highly intelligent white female of approximately 54 years of age. The head and neck presented no abnormalities. The blood pressure was systolic 110, diastolic 60. The temperature was normal.

Physical examination, except of the right breast, was essentially negative.

The right breast showed a large mass at the position of ten o'clock; the mass was adherent to the skin and there was definite puckering of the skin. There was neither retraction of nor discharge from the nipple. Transillumination of the breast confirmed the opinion that a large semisolid tumor occupied the right upper quadrant of the breast. There were a few hard glands palpable in the right axilla.

Roentgenograms of the chest and spine were negative and the various other laboratory studies made yielded essentially normal findings.

A specimen of tissue removed from the right breast proved the tumor to be adenocarcinoma of Grade IV malignancy.

A radical right mastectomy was done by one of us (W. H. P.). At surgery several glands along the course of the subclavian vessel were found enlarged and were removed. These on biopsy were found to be malignant, showing an adenocarcinoma, Grade IV.

Pathologic report by Dr. John C. Henthorne: Right breast, adenocarcinoma, Grade IV, 6.0 by 3.0 by 3.5 cm. Diffuse involvement of axillary nodes. Subclavian node, early involvement of one node by metastatic carcinoma.

It was necessary at surgery to remove so large an area of skin that secondary grafting was required. The patient at discharge from the hospital was in good condition. It was estimated that this patient had received a total of approximately 200,000 units of theelin. It is felt that the prognosis is exceedingly poor.

#### CONCLUSIONS

Many able investigators have been able to produce, employing strains of mice capable of developing spontaneous mammary carcinoma, malignant neoplasms of the breast in male mice by continued estrogenic therapy. It has been possible also to reduce the age level at which such strains would ordinarily develop adenocarcinoma of the breast. Other investigators have produced malignant lesions of the breast in rats

possessed of no hereditary tendency to the development of spontaneous cancer. Still others have shown that human beings under prolonged estrogen therapy undergo definite breast and genital changes, which may eventually lead to malignant lesions.

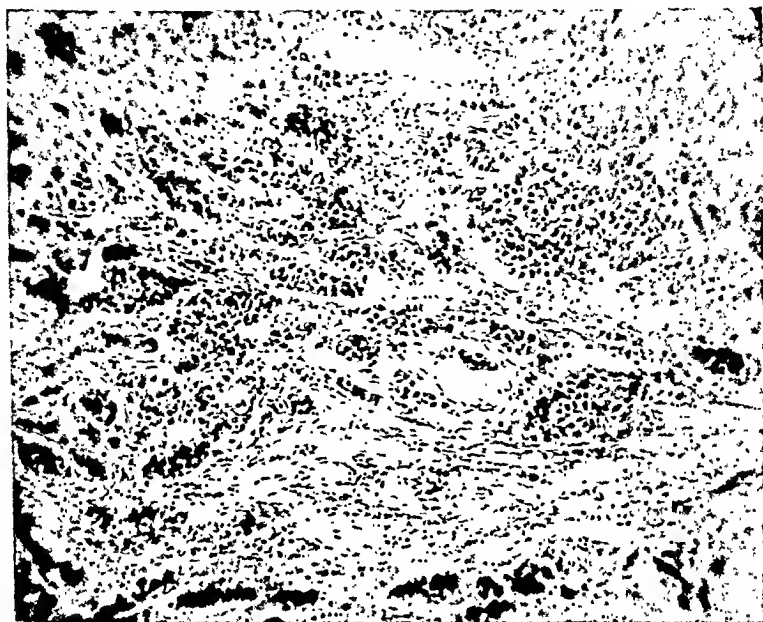


Fig. 1.—Photomicrograph of mammary carcinoma (hematoxylin-eosin stain,  $\times 150$ ).

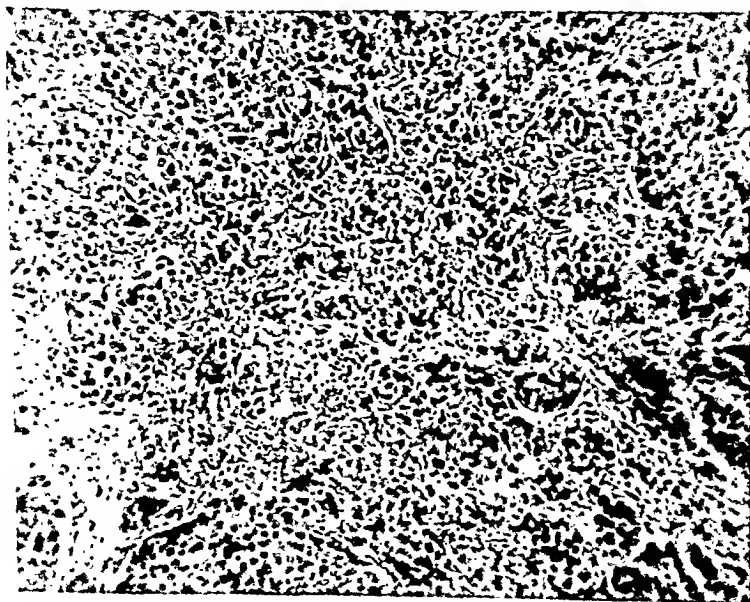


Fig. 2.—Axillary lymph node metastasis from breast carcinoma (hematoxylin-eosin stain,  $\times 150$ ).

At the present time it would seem unwise to draw definite conclusions regarding the actual production of malignant lesions in the human being as a result of prolonged or massive estrogen therapy. Before such a position would be tenable, more careful study will be necessary to evaluate the already accumulating case reports, but from the evidence now at hand it would seem that the indiscriminate use of the hormones is certainly not beneficial to the majority of the patients on whom they are used and may actually be harmful. Certainly they should be employed with judicious care.

In the case reported here, although again definite proof of the role of the estrogens is lacking, one would suspect at least that the estrogens may have played a very major etiological role in the development of the malignant adenocarcinoma that was present in the breast.

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# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## CHRONIC INTRA-ABDOMINAL LYMPHADENOPATHY

WITH SPECIAL REFERENCE TO CHRONIC NONSPECIFIC  
MESENTERIC ADENITIS

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UP UNTIL recent years intra-abdominal lymphadenopathy has never received the attention which equals in any way that which lymphadenopathy in other parts of the body has received. In a previous communication a study of the acute forms of intra-abdominal lymphadenopathy resulted in the following conclusions:

General abdominal lymphadenopathy reflects a similarity to other lymphadenopathies in different regional areas. In the abdomen many of them are parts of distinct symptom complexes, such as typhoid fever or dysentery. Others are related to loosely gathered clinical entities known collectively as the rheumatic group. Still others are related to various groups associated with generalized cutaneous manifestations including some of the exanthemas. A large group seems to be related to a preceding catarrhal or throat infection and this seems to have some relationship to forms of glandular fever and infectious mononucleosis and to what is clinically known as abdominal grippe. Finally there is a group in which the lymphadenopathy cannot be clinically connected with any demonstrable preceding or accompanying lesion. Because of this fact the cases in the latter group have been associated in a still undemarcated and undifferentiated group and are called nonspecific adenitis for want of a better nomenclature.

Not always is the causative agent demonstrable in nonspecific mesenteric adenitis. In only a minority of the latter cases bacteria can be demonstrated in the glands, and the predominating organism is some strain of streptococcus. Occasionally other bizarre organisms can be cultured, such as *Bacillus melitensis*. An unidentified virus has also been suggested as the causative agent, but the correlation of this virus with that which might cause poliomyelitis has not been proved. No relationship can be demonstrated by the Frei test with lymphogranuloma venereum; and, although various parasites have been found to occur in the intra-abdominal lymph nodes, a causal relation cannot be established between them and acute nonspecific mesenteric adenitis.

The portal of entry for the causative agent for acute nonspecific mesenteric adenitis is only on rare occasions the appendix, and this can

happen only because of some anatomical abnormality of the lymphatic drainage pathways of the appendix. More commonly the portal of entry seems to be related to catarrhal or throat infections and then acute nonspecific mesenteric adenitis is least commonly a manifestation of a hematogenous mechanism; or, more commonly, the causative agent is swallowed from the oropharynx and passed along to the terminal ileum from which local absorption occurs. Most often of all the nonspecific mesenteric adenitis is a local absorption effect from some local nondemonstrable lesion in the ileal segment of the alimentary canal. It can be safely assumed that this includes various forms of transient enteritis and other surface infections, aided and abetted by various gross and microscopic injuries and other forms of physical and chemical trauma.

In this most common mechanism the similarity to the ordinarily observed phenomena in cervical adenitis is absolute. In either case local injuries and infections permit the passage of the causative agent to the appropriate lymph nodes. The mechanism is based upon an exact duplication in either position of the anatomical arrangement of the local lymphadenoid tissue in the wall of the alimentary canal and the corresponding lymph nodes. The heaping up of extraordinary collections of lymphadenoid tissue in the wall of the alimentary canal at either of these locations is remarkable and seems important from an etiological and mechanistic viewpoint.

*The Lymphadenoid Tissue.*—The important role played by the lymphadenoid tissue of the alimentary canal in all forms of mesenteric adenitis is correctly appreciated only when one realizes the great frequency with which it becomes involved in the various diseases known to clinical medicine. This tangible knowledge indicates an astonishingly large incidence of involvement of the mesenteric glands in typhoid and paratyphoid fever, in the various forms of bacteremia, in status lymphaticus, in tuberculosis, rarely in syphilis and actinomycosis but more commonly in the various blood dyscrasias, in a case of agranulocytosis reported by Felsen,<sup>37</sup> and in the various forms of colitis, enteritis, and dysentery. This list does not include the various forms of malignancy and such borderline lesions as Hodgkin's disease. In some of these, such as typhoid fever, the mechanism of development and the path of transit of the infection are well known. The newer anatomical knowledge in colitis and dysentery indicates a fairly close approximation to the latter.

In all forms of diarrheal disease in infants and children (infantile diarrhea, cholera infantum, acute ileocolitis in infants and children, summer diarrhea, etc.), the process seems centered in or shows a predilection for the vicinity and substance of the intestinal lymphadenoid collections and is especially marked in Peyer's patches. Apparently all of these forms begin as surface infections and reach down into the substance of the intestinal wall as the pathologic process proceeds. The

spread into the wall occurs along the lymph channels (i.e., lymphangitis) into collections of lymphadenoid tissue (solitary follicles, Peyer's patches). Wherever in the various publications (Holt,<sup>50</sup> Felsen,<sup>37</sup> etc.) particular attention is paid to this element and the findings recorded, it is astonishing to see how much and how often specific mention is made of the localization about and the involvement of Peyer's patches. In this regard the differentiation between small and large intestine is merely a quantitative one and depends upon the distribution of solitary and aggregated collections of lymphadenoid tissue (solitary follicles, Peyer's patches). In the small intestinal cases it is common to find the lesion localized for the most part and/or limited to the lower ileum where the lymphadenoid tissue abounds to such a large extent in the intestinal wall. The spread into and the involvement of the adjacent tissues of the intestinal wall become visible only with the prolongation of the illness into a relatively chronic stage and with its anatomical development.

So-called catarrhal infections are commonly associated regionally with the upper reaches of the alimentary canal and have been previously referred to under the general nomenclature of throat infections. For the most part these occur anatomically in relation to the lymphadenoid apparatus of the tonsils and adenoids and their secondary lymph node involvements occur in the anatomically related cervical glands. They are commonly said to be surface infections. Whether such catarrhal infections can occur deep down in the ileum and originate in and about the Peyer's patches is something which is apparently beyond the present available powers of demonstration, but certainly it is so that in simple mesenteric adenitis without other demonstrable lesions there are identical symptomatic and anatomical manifestations to those similar lesions that originate in the oropharynx, and this assumption cannot be denied. The interplay of throat infection with abdominal symptoms as indicated in the previous communications is more than a mere coincidence and is remarkable.

The previous communication<sup>11</sup> on acute abdominal lymphadenitis summarized all of the available knowledge concerning the anatomy and physiology of the intra-abdominal lymph nodes. This included the usual type of structural arrangement and its "normal variations." The normal functional processes (physiology) and the ways in which these processes are affected by age, nutrition, environment, growth, etc., and certain abnormal conditions of the body, such as fever, anemia, etc., were all gone into very exhaustively. It does not seem necessary to repeat this factual knowledge and those interested sufficiently are referred to the original paper or to the standard works on anatomy and physiology. It seems important, however, to comment again upon the variable size of the nodes when distinguishing between normal and abnormally enlarged glands and this factor is especially important in

long-standing or chronic conditions. It seems that there are as yet no certain measures of the normal variation in size of the mesenteric and other lymph glands. Mead's<sup>89</sup> paper and Hellman's<sup>56</sup> investigations and numerous other observations referred to by Strömbeck<sup>127</sup> on soldiers killed in World War I show that the lymphatic tissue and glands may be considerably more developed than have hitherto been assumed. In my previous study<sup>141</sup> I have stressed this anatomical variation and have pointed out the possibility which cannot be totally excluded: that in many of the published cases the size of many of the observed intra-abdominal glands may have possibly been within normal limits, that errors in interpretation therefore could easily have been made, and that, as a consequence, fundamental errors of diagnosis were possible in the reference of any observed symptomatology to such lymph nodes.

It seems important also to comment again upon the superlatively developed absorption function of the intestinal tract, which, combined with the constant presence of bacteria in the intestinal lumen, creates a situation in which the passage of bacteria from the bowel interior into the associated lymphatic vessels and glands must be considered an almost normal and physiologic phenomenon. Although manifestations of the reaction of the host's defense mechanism against this continuous onslaught of bacteria (i.e., disease) is not apparent, it must be true that lymphatic enlargement will take place and in certain instances persist. In the ordinary stress of health and disease and under the proper circumstances this would tend either to encourage reference to or to complicate attempts at integration of the presence of enlarged mesenteric nodes into a given symptom complex in which other pathology is not demonstrable.

#### CHRONIC INTRA-ABDOMINAL AND/OR MESENTERIC LYMPHADENITIS

In contradistinction to the discussion of acute abdominal lymphadenopathy made previously, the material in this communication refers to chronic forms of abdominal symptomatology. In this communication the term chronic refers to symptoms referred to in the interior of the abdominal cavity which have lasted a relatively long time, or which have occurred as a succession of episodes interrupted by periods of lesser intensity, perhaps almost to the point of complete disappearance. The appearance of such episodes as acute or subacute phenomena must under such definition be interpreted as acute or subacute exacerbations of the underlying cause of the abdominal pain.

Chronic abdominal symptomatology in this communication will have no reference to that associated with early or late malignancies of any kind; nor with forms of hypertrophic growth, such as Hodgkin's disease, lying in the borderline of nonmalignant and malignant pathology; nor with continued manifestations associated with definite diseases of neurologic spinal and peripheral nerve apparatus. Infections with the tubercle bacillus, with the *Spirochaeta pallida*, or with other such ex-

tremely specific forms of inflammation will be referred to as the occasion seems fit. But, in the main, this communication refers to abdominal symptoms caused by inflammatory changes produced by the ordinary forms of pyogenic bacteria. The ultimate purpose is to explain certain chronic abdominal symptom complexes as being caused by chronic inflammatory effects in the abdominal and especially in the mesenteric lymph nodes alone or as a consequence of certain complications which can secondarily occur; and, conversely, to stress the importance of the lymphatic apparatus in the production of chronic abdominal disturbances. In this regard this communication forms a corollary to the previous communication on acute nonspecific mesenteric adenitis.

In view of past experiences one cannot fail to be impressed with the frequency with which the elucidation of the origin of certain chronic abdominal symptoms still remains impossible; this in spite of the vast strides which have been made in abdominal diagnosis. With modern methods and modern instrumental and laboratory aids the number of such unexplainable cases has gradually grown smaller and smaller, but, nevertheless, there still remains a large group in which this disability still exists and in which recurrences of symptoms follow operation.

It has been too easy to ascribe these nonsuccesses to hysterical or neurasthenic bases in the subjects who presented themselves with these symptom complexes, but, as experience grew, it became possible to markedly restrict any neurogenic origin and to classify cases with chronic or recurrent abdominal symptoms somewhat as follows:

1. A large group in which adequate study is able to demonstrate a urologic lesion and in which a definitely good result follows the correct form of therapy.

2. A smaller group in which it is possible to demonstrate (a) the presence of gallstones or (b) the absence of a roentgenographically visualized dye-filled gall bladder, in either case with or without clinical or other evidence of any inflammatory change. In spite of the possible history or observation of definite attacks of gall bladder or hepatic colic, it is universal experience that in about 10 per cent or more of such cases recurrences of symptoms have followed the operation of cholecystectomy in which a satisfactory cause of the original and of the recurrent symptoms apparently could not be demonstrated.

3. A group in which abdominal pain could be finally correlated with female pelvic disease of one kind or another.

4. The largest group in which the appendix is said to play a role and in which a classification of the available facts yielded the following:

- a. A group in which operation (appendicectomy) was not done in the acute stage of a bona fide acute appendicitis (acute suppurative, acute gangrenous, acute empyema, acute perforative appendicitis, etc.). For one reason or another the symptoms continued for a variable length of time into a chronic phase until the appendix was removed at a later

period. The usual conditions found were a chronic abscess or chronic hypertrophic forms of appendicitis in some cases approaching the lesion of nonspecific granuloma of the intestine. An invariable cure followed.

b. There was a small group in which it was said that the pain resembled that of gastric and duodenal ulcers but in which the symptoms were referred to the appendix without, however, any pathologic lesion being demonstrable therein. In almost countless experiences this has been proved to be a delusion. The pain had no demonstrable relation to the appendix or to the stomach and duodenum and no other demonstrable basis. In practice it was most difficult to handle and never reacted to any therapeutic agent which was employed.

c. Another group consists of cases in which the main symptom was unrelievable episodes of or continuous annoying, sticking pains in the right side of the abdomen without the symptoms simulating any well-known complex. Appendectomy and other forms of therapy were of no help.

In later years it has seemed to be more and more true that many, if not all, of the cases in Groups b and c had some form of psychoneurotic basis and background for the clinical picture. It was frequently suggested by the presence of corneal and pharyngeal anesthesia and by excessive activity of the knee and other tendon reflexes.

d. This large group consists of cases in which an obliterated appendix was removed. Commonly this was associated with a somewhat hypertrophic change in the terminal nerves of the appendix which was labeled a neuroma. Recurrences of symptoms were almost the rule and I am convinced that such anatomical changes are of regressive involutionary character and cannot produce any abdominal pain.

5. In the last decade attention has been focused on a group of cases in which abdominal symptomatology has been demonstrably associated with enlargement of the mesenteric lymph nodes. The previous numerous discussions have considered only the acute episodes of mesenteric lymphadenitis. It is the purpose of this communication to call attention to the chronic forms of mesenteric lymphadenitis.

Considering the subject from an entirely different approach, it seems:

1. That there are certain abdominal manifestations that are common in adults and practically unknown in infancy and early childhood, such as those of chronic gastritis, ulcer and carcinoma of the stomach, biliary colic, gastric crises in tabes dorsalis, and movable kidney. Appendicitis is apparently a great rarity in the first and even the second year.

2. That there are some abdominal symptom complexes that have the same significance and the same characteristics at all ages, or at least in older children and in adults, such as salpingitis, appendicitis, and renal colic.

3. That other abdominal manifestations occur wholly or predominantly in infancy and/or early childhood. Those occurring in infancy

are nearly all produced by obstruction of a hollow viscus (pyloric stenosis, intussusception) or are associated with digestive abnormalities (colic). Later abdominal pain occurs with throat infections and with pneumonia, but this is relatively acute. Chronic abdominal pain occurs with tuberculous spondylitis, nonappendiceal forms of peritonitis, multi-form pains of tuberculous peritonitis, abdominal pain that accompanies rheumatism and Henoch's purpura, the occasional case of chronic pain due to worms, and chronic pain and symptoms due to enlarged inflamed mesenteric and retroperitoneal glands.

#### CLINICAL PICTURE OF CHRONIC MESENTERIC ADENITIS

There is a form of long-standing chronic abdominal disease in which patients complain of vague and diffuse intermittent transitory attacks of colicky, drawing or dragging pain in the right lower quadrant or other regions of the abdomen commonly associated with anorexia, with repeated attacks of indefinite gastric distress associated with nausea and vomiting, with loss of weight, and with slight fever. Constipation and diarrhea are not common symptoms in the chronic form but may be present in the characteristic acute exacerbations which occur. And according to Alvarez<sup>2</sup> a subacute form of arthritis finally follows in some. The symptoms occur similarly in older children and in young adults and more commonly in the female sex.

In the more advanced cases and in the older group there is a tendency toward marked mimicry of other known symptom complexes. There may be symptoms of dysphagia (Wakely<sup>136</sup>), or symptoms suggestive of peptic ulcer (Thiemann,<sup>120</sup> Lund,<sup>83</sup> Bier,<sup>10</sup> Keppler and Erkes,<sup>71</sup> Davidovitch,<sup>31</sup> Ljunggren,<sup>81</sup> Golden and Reeves<sup>47</sup>), of biliary colic (Most,<sup>34</sup> Pribram<sup>108</sup>), of intestinal spasm (Schalij<sup>118</sup>), of constipation or diarrhea (Sternberg<sup>125</sup>), of renal colic or hematuria (Schmieden,<sup>121</sup> Walker,<sup>137</sup> Davidovitch,<sup>31</sup> Golden and Reeves<sup>47</sup>), or even of sciatica (Ljunggren<sup>81</sup>). The most common symptom complex imitates very closely that which we customarily have known as chronic appendicitis.

Whenever such a patient is explored by abdominal incision, there is found scattered throughout the mesentery a variable number of enlarged lymph nodes. Not always are there evidences of any distinct inflammatory process, and on histologic examination, the majority of such enlarged lymph glands will reveal a cellular and sinus hyperplasia of their interior structure. The immediate impression is that the lymph gland enlargement is due to some long-standing (chronic) form of infection of immediately undeterminable etiologic classification. Nevertheless, for a long time thereafter the patient will be watched further, possibly under the suspicion that a true Hodgkin's disease will later be recognizable, but further and prolonged observations do not bear this out.

In this type of symptom complex there is much evidence to show that a chronic mesenteric adenitis is the cause. Struthers,<sup>128</sup> Freeman,<sup>44</sup>

and Hutchison<sup>64</sup> have all emphasized the role of mesenteric lymphadenitis in the causation of abdominal pain in children. Such an adenitis can best explain the associated tenderness and spontaneous pain, as in inflamed glands anywhere, here, due to irritative colic producing peristalsis, the predominance of pain about the center of the abdomen and the lower right quadrant, which seems a favored region, and the occasional persistence of pain and tenderness long after the primary infection has apparently ceased to be active.

Occasionally such glands are sufficiently large to be palpable. In influenzal infections Brennermann<sup>17</sup> reports that extensive mesenteric adenitis is a frequent finding in post-mortem examinations, and more and more commonly, as attention is being constantly focused on this, enlarged glands form the sole findings at abdominal explorations either performed frankly as such or done under mistaken diagnoses.

The pain may vary from a dull, grumbling discomfort, usually in the right lower quadrant, to attacks so violent that surgical intervention is considered. The mechanism by which this pain is produced in uncomplicated cases has never been fully explained. Inflammatory irritation of the peritoneum over the node and mechanical irritation of nerve fibers in the mesentery with disturbed visceral physiology have been suggested (Golden and Reeves<sup>47</sup>). Evidence of the former is usually lacking at operation. The possibility of the latter is suggested by the colicky character of the pain in some cases together with absence of disease of the intestine itself.

The periumbilical coliclike pains, which according to some are characteristic of mesenteric adenitis, are ascribed to reflex intestinal spasms or partial invaginations (Tyrrel-Gray, 1922<sup>131</sup>) which cause an abnormally strong pull on the mesentery. According to others even a normal postprandial peristalsis may give rise to similar pains if the mesentery has become abnormally sensitive owing to the enlarged glands (Goldscheider<sup>48</sup>). Brüning (1921-1922),<sup>20</sup> on the other hand, considers that the pain is caused in the intestinal wall itself, but this opinion has not yet been generally received.

Intestinal spasm and invaginations have been observed in cases of mesenteric lymph gland enlargements. Carson (1918)<sup>22</sup> presents two cases in which he found in children partial spontaneous invaginations with the starting point corresponding to the site of the glandular alteration. Braithwaite<sup>15</sup> (1926) describes an operatively demonstrated limited spasm in the lower part of the ileum just opposite a calcified gland surrounded by reddened serosa and situated close to the free border of the mesentery.

The vast majority of these cases occur in children and in the female sex so that this may be accepted as more or less characteristic of this affection. It is difficult to say how frequently this form of chronic lymphadenitis occurs. In Foster's<sup>42</sup> series of cases in which he has

grouped acute and chronic cases, it seems remarkable that the percentage for the chronic cases is 64 as opposed to 8 per cent for the acute cases. My own experience is not large, when the cases which have received operative or other proof only are considered, because, ever since my attention was first attracted to this lesion, I have consistently refused to operate upon cases with any such symptomatology unless and until the observable phenomena were so strong and so acute as to render operation compulsory. Consequently the number of proved cases of my own are too few in number and I have possibly escaped making an undue number of errors.

Then, too, the observable anatomical facts are frequently and commonly not so easy to differentiate and classify. Commonly one questions the role of tuberculosis or suspects an early stage of Hodgkin's disease or other form of lymphatic malignancy. It may happen that one is not impressed with the presence of enlarged glands and dismisses them lightly as of no importance. Therefore a correct impression of the relative and actual number of cases of simple chronic mesenteric lymphadenitis may not be made until a much larger diversified number of adequately proved cases is available in the composite experience.

The differentiation between acute and chronic cases is sometimes more or less of an artefact, because at times the chronic cases are simply those in which a succession of acute episodes has taken place separated by intervals in which the symptomatology is less intense or in which it has simmered down even to the point where the symptoms are tolerated so completely as to make the patient believe they have disappeared entirely. In either case chronic anatomical changes eventually characterize the pathologic picture. This probably accounts for the peculiar percentage figures in Foster's<sup>42</sup> series.

Commonly roentgenographic study of the abdominal viscera (gastrointestinal series, etc.) shows no abnormality.

Under the usual normal condition, roentgenographic observation shows that the stomach empties continuously and barium passes steadily in the normal direction, reaching the cecum in one and one-half to four hours. Each successive film shows progress distally in the position of the head of the barium column. The segmental peristaltic movements flow smoothly and are promptly followed by normal flexible relaxation of the intestinal wall. If there is no delay in movement, the ileum should be empty in nine hours. The barium mass in the normal small intestine is usually continuous; that is, it is not broken up into separate small oval boluses. The width of normal, barium-filled loops varies from 1.5 to 3.0 cm. and is usually 2 to 2.5 cm.

In association with acute symptoms Golden and Reeves<sup>47</sup> observed the following manifestations of disturbed small intestinal physiology:

"(1) Localized spasm, i.e., narrowing of a small segment adjacent to the calcified node, either temporary following a peristaltic wave, or per-

sistent; (2) persistent generalized spasm of a group of small intestinal loops in the region of the diseased nodes; (3) delay in the passage of barium at the site of the calcified node; (4) delay in the emptying of the ileum for periods of over nine hours."

In a certain number of the cases areas of calcification are visualized roentgenographically. Golden and Reeves<sup>47</sup> point out the possibility that the roentgenographically observed physiology in the intestine may be an explanation for the symptoms often associated with calcified mesenteric lymph nodes: "These disturbances in small intestinal physiology seemed to take place in loops of intestine directly adjacent to calcified nodes. The puckering and contraction of the mesentery about them and the distortion of the blood vessels make it seem very likely that the nerve fibers are involved in the process. One manifestation of abnormal intestinal physiology observed in these cases is spasm, and spasm of the intestine offers at least one possible explanation for pain. Occasionally a patient says that pressure on the calcified node reproduces the pain for which relief is sought."\*

This presents an acceptable mechanism for the initiation of such disturbances in intestinal physiology. However, one should always remember to keep a questioning attitude concerning the relationship of roentgenographically demonstrated calcified abdominal lymph nodes and the symptom complex which an individual patient presents because it is not necessarily so that the one causes the other.

#### ETIOLOGY OF CHRONIC MESENTERIC ADENITIS

I refer again to my first communication<sup>141</sup> in which a complete résumé of the factual knowledge regarding acute mesenteric adenitis is made. This is necessary because any acute condition may theoretically, and in some of the cases actually does, pass into a chronic phase. For purposes of clarity the various etiological factors will be listed again and the relationship of any of them to chronic symptomatology will be made and emphasized.

1. *General Factors.*—A list of the agents which can cause generalized lymphadenopathy in which the mesenteric glands may take part includes many others besides those in the following groups:

a. The first group include infections of the upper respiratory tract, glandular fever (infectious mononucleosis), some of the exanthemas, typhoid fever, and influenza. These are distinctly acute infections which very rarely go into a chronic stage.

b. The second group include tuberculosis, syphilis, many cutaneous diseases, poisoning due to certain metals, marked inflammation or ulcers of the intestines, especially those of long duration, actinomycosis, rickets, scurvy, status lymphaticus, and miscellaneous foci of infection of var-

\*Compare this with the discussion under tuberculosis of the mesenteric nodes.

ious types. While all of these necessarily must have a beginning which might possibly be interpreted as an acute stage, they are all best known in their chronic manifestations and should more correctly be considered as such.

c. A third group of lymphadenopathies are associated with leucemia, sarcoma, Hodgkin's disease, and carcinoma and these are rightfully outside of the subject under discussion.

2. *Lymphatic Block Around the Appendix (Royster<sup>116</sup>)*.—If such an anatomical abnormality would have any effect, it would no doubt be followed by chronic symptoms. Nevertheless I know of no specific case either in my own experience or in other literature in which this etiological factor was indubitably proved.

3. *Trauma*.—Except for Wagner's<sup>135</sup> possibly not very conclusive case, there is no other experience along these lines. Compensation courts have ruled, however, that trauma can be a competent producing cause for abdominal symptoms. Nevertheless, in scientific medical circles the evidence of properly controlled scientific observation is needed before this ruling should be approved.

I include the notes of the only case of this kind in my experience, even though the case can not be classified as acute. I do so, wishing to put this case on record because of any medicolegal value it may have and because it illustrates the want of scientific basis for any etiological assumption.

A 7-year-old girl sustained a moderately severe fall and landed squarely on her buttocks. Immediately thereafter she complained of severe abdominal pain and during the remainder of the day she vomited several times. The next day the pain grew less and the temperature remained normal. On the following day, however, the pain returned and the temperature rose to above 102° F. The family physician noted that there was tenderness and a boardlike rigidity and that the patient screamed with pain during the examination. When I examined her, the breathing seemed diminished abdominally and I confirmed the other abdominal findings. The indication led us to operate immediately: (1) because we could not evaluate correctly the role of the initial trauma and we feared its possible consequences, and (2) because the picture was that of a bona fide acute appendicitis of more than mild or moderate severity. The exploration, however, showed no sign of any intra-abdominal injury and no macroscopic evidence of an undoubted appendicitis, but a large number of swollen mesenteric lymph nodes with a moderate serous peritoneal exudate. The appendix was removed. The patient's temperature gradually fell to normal as is usual in any lymphangitis elsewhere in the body and an uneventful recovery followed.

4. *Allergy*.—It is difficult to avoid involving an allergic mechanism in the chronic cases in which the symptomatology consists of a succession of episodes which sometimes increase progressively in severity and in acuteness. Kleiber's<sup>72</sup> experiments in Pribram's Clinic in Berlin furnish an explanation of the recurrences of local inflammatory processes

along allergic lines. I am very much inclined to accept this mechanism as an adjuvant factor in at least some of the cases of this kind.

5. *Parasites*.—The role of intestinal parasites in the etiology of acute mesenteric adenitis was extensively discussed in my previous communication on that subject. In young children who harbor these parasites abdominal complaints are frequent and enlargement of the mesenteric glands has been noted. In some of the chronic cases at least (in contradistinction to the acute cases), there seems to be a distinct causal relation between the parasites and the lymph gland enlargement. The usual habitat of the worms is the lower part of the ileum and the appendix and the cecum, which I believe are the ordinary starting points of lymphadenitis.

6. *Rheumatic, Erythema, Purpura, etc., Groups*.—Individual cases are prone to a symptomatology that extends over a considerable time so that they are customarily known as chronic conditions. Occasionally, as pointed out in the previous communication on acute mesenteric adenitis,<sup>141</sup> the post-mortem examination of fatal cases reveals an unexpected enlarged condition of the intra-abdominal and mesenteric nodes in which streptococci are sometimes demonstrable. While the course of the dominating disease (rheumatic, erythematous) is of long duration (chronic), it seems that such glandular enlargements are probably due to added bacterial infections to which the generally debilitated condition of such individuals makes them prone. Chronic mesenteric adenitis occurs in certain specific infections.

7. *The Dysentery Group*.—This is a chronic affliction marked by more or less numerous exacerbations and recrudescences of infection in which an allergic mechanism undoubtedly plays an important part. In the acute episodes the associated lymph glands are swollen and hyperplastically inflamed. A good deal of retrogression occurs in the intervening periods between the acute manifestations. The glands, however, never reach normal and a chronic adenitis remains. This is a specific form of chronic mesenteric adenitis.

8. *Nonspecific Granuloma of the Digestive Tract*.—In certain quarters it has been suggested that this is the terminal stage of dysentery (Hurst,<sup>63</sup> Felsen,<sup>37</sup> and Winkelstein<sup>142</sup>). In my previous communication<sup>141</sup> I came to the conclusion that these chronic granulomatous lesions result from a variety of preceding conditions. The essential lesion demonstrable in operating room and autopsy specimens is an interstitial lymphangitis of the bowel wall with miliary foci of suppuration, and with secondary scarring, thickening, and contracture. This lesion also is marked clinically by exacerbations and remissions, and the condition of the associated intra-abdominal lymph glands follows closely the age and the stage of activity of the intestinal lesion so that a chronic adenitis is present. If one takes the view that nonspecific granuloma of the intestine is the end product of some specific infection such as dysentery, the associated chronic adenitis may very well be considered as a specific

lesion. If, however, one takes the view that the lesion results from a multiplicity of preceding conditions, the chronic adenitis is truly a nonspecific one.

9. *Infection With Filterable Viruses.*—I have no experience nor have I been able to find any experience in the literature of the relationship of any form of chronic mesenteric adenitis to infection with a filterable virus.

10. *Lymphogranuloma Form of Infection.*—This may have an acute beginning and an acute phase, but in clinical medicine it is best and most widely known as a distinctly chronic affection lasting for a considerable length of time.

The suggestion that chronic mesenteric lymphadenitis might possibly be due to the same cause as lymphogranuloma venereum seems indicated by the following factors: that frequently there is a history or evidence of a primary lesion (Thompson<sup>130</sup>), that frequently lymphogranuloma venereum is an extragenital occurrence (David and Loring<sup>30</sup>), that this disease may cause a generalized lymphadenopathy (von Haam and D'Aunoy<sup>134</sup>), and, finally, that cases of lymphogranuloma venereum have been reported in which involvement of the retroperitoneal lymph nodes was found at autopsy (Kondo,<sup>74</sup> Reichle and Connor,<sup>111</sup> and Kornblith<sup>75</sup>). In twelve cases of mesenteric adenitis which were explored under the diagnosis of appendicitis in Ireland's<sup>65</sup> series the Frei test yielded a negative reaction. In these, therapy with lymphogranuloma venereum antigen, as employed by Bloom,<sup>12</sup> or with solganal (the disodium salt of 4-sulfomethylamino-2-auromercaptobenzene-1-sulfonic acid), as employed by Gohrbandt,<sup>45</sup> was not used to make a diagnosis.

11. *Relationship to Syphilis.*<sup>\*</sup>—In all the experience which I have had in many hospitals and in private practice in which all patients have been subjected routinely to Wassermann and Kahn tests, I do not remember ever having seen a single case in which syphilitic infection could be assigned as a cause of the mesenteric enlargement. This seems to be in agreement with all other reported experience.

12. *Actinomycosis.*—In the abdominal form of actinomycotic infection localizing in the general neighborhood of the ileocecal junction, chronic enlargement of the associated lymph nodes occurs.

#### BACTERIAL INFECTION

The experience in the acute cases is sufficiently strong to show that bacterial infection is the most common cause of mesenteric adenitis. The same undoubtedly must be true of chronic mesenteric adenitis. The intestinal tract has seemed to be the most obvious source of infection and the most probable route through which bacteria have been trans-

\*The relationship of tuberculous infection is discussed subsequently in this communication.

mitted to the mesenteric lymph nodes. Because this aspect is not adequately appreciated by the profession in general and possibly particularly by pediatricians, it needs repeated emphasis.

The increase in the number of gastrointestinal infections is coincident with the average time of weaning. This is probably due to a change in diet through which contaminated foods may invade the intestinal tract, and it is interesting to note that this period immediately precedes the time of life in which mesenteric adenitis appears.

There are reasons for believing that the intestinal mucosa is more permeable in childhood than in adult life. At any stage of life bacteria are constantly passing through the wall of the bowel. The lymphatics of the mesentery constantly contain these absorbed bacteria and the nodes near the spine (mesenteric, ileocolic, etc., groups) are the first to block the further passage of the organisms and constitute one of the most important lines of defense. This bacterial invasion appears to be most active in the lower end of the ileum and in the cecum, because in this region the intestinal contents still contain fairly large numbers of bacteria and the process of absorption reaches its maximum activity. That the presence of such numbers of organisms in the intestinal and mesenteric lymphatic apparatus is not always an innocuous phenomenon is not to be doubted, and it seems highly probable that many of the strange disorders of digestion that are associated with slight fever, nausea, bloating, abdominal soreness, signs of reverse peristalsis, diarrhea, inanition, and arthritis could best be explained on the basis of nature's reaction to the presence of bacteria and their elaborated toxins and that this indicates a subacute or low-grade type of lymphangitic infection.

The usual organisms which can be demonstrated in the interior of the biopsied lymph nodes belong to some strain of streptococci in the nonspecific cases. According to Alvarez,<sup>2</sup> it seems that because of the increasing frequency with which infection with *Brucella abortus* and *Bacillus tularensis* takes place, it may be found that these organisms also account for some of the cases of mesenteric adenitis. Diagnostic tests are now available to facilitate this differentiation.

#### TOXEMIA

The idea that a toxin, either of bacterial or possibly of other origin, is the cause of enlargement of the glands in the mesentery has received much comment and was discussed in my first communication on acute mesenteric adenitis.

*Nonbacterial Toxemia.*—The earliest reference which I have been able to find in regard to any possible nonbacterial origin of any toxin absorption is the Paris Thesis of Brian.<sup>18</sup> The latter associates a non-specific mesenteric adenopathy with intestinal stasis on the basis of an entire absence of definite anatomical, bacteriological, or other laboratory factors. I have had no experience in which this etiology could pos-

sibly be assumed. Even granting the correctness of the assumption here, the possibility of associated bacterial action being the true originating mechanism for the toxin production and absorption and for any secondary lymphadenopathy is highly probable. Should the acute phase of the infection not be terminated spontaneously or with adequate therapy, a chronic phase undoubtedly would follow in which stasis and bacterial activity aid and abet one another. If this mechanism should prove to have the importance which some people associate with it, it must undoubtedly be true that it will be most commonly found in association with a chronic form of mesenteric adenitis.

Intestinal stasis associated with distention and surface inflammation and abrasions has been mentioned as producing portals of entry to the mesenteric lymph nodes (Bell<sup>8</sup>), and it has been suggested that the resistance of the mucosa to the passage of organisms is lessened by the absorption of chemical intestinal toxins (Thiemann,<sup>129</sup> Carson,<sup>22</sup> and Wilensky<sup>141</sup>).

Adami,<sup>1</sup> Alvarez,<sup>2</sup> and Heyd<sup>58</sup> have stressed the importance of a form of acute intoxication associated with visceroptosis, chronic constipation, intestinal stasis, and ileocecal valve incompetence. Visceroptosis and/or constipation were noted by Foster<sup>42</sup> in 27 per cent of his cases. In one case chronic mesenteric adenitis was actually observed. Of these various factors incompetence of the ileocecal valve has received a good deal of controversial attention.

Kellog (1913)<sup>70</sup> considers that the latter condition is a "serious cause of disease." Castex, Romano, and Beretervide (1925),<sup>23</sup> Valerio (1926),<sup>133</sup> and Harrenstein (1926)<sup>54</sup> all are of a similar opinion. Other authors on the other hand, e.g., Rosanoff (1923)<sup>115</sup> and Odermatt<sup>98</sup> (1926) are of the contrary opinion.

Modern knowledge tends to emphasize the dominating role of a sub-acute or chronic infection of the bowel as the most causally important part of any such anatomical or physiological abnormality. Whatever opinion one may have as to functional disturbances of the ileocecal valve and their importance for the origin of abdominal symptoms, it cannot be denied that regurgitation of cecal contents must promote ileitis in the lower part of the small intestine by virtue of the additional infection which it must surely introduce.

Bezeeny,<sup>9</sup> in 1933, reported the finding of histamine-like substances in lymph vessels which can cause a type of inflammation comparable to lymphangitis. According to Foster,<sup>42</sup> in persons who have sedentary living habits, who suffer from constipation and visceroptosis, and who overeat, such an accumulation of poisons resembling histamine might occur and could cause chronic changes in the mesenteric lymph nodes, with their resulting flare-ups into an acute disease syndrome at the time of definite points of saturation or when fortified by added transient bacterial insult.

*Bacterial Toxemia.*—Bell<sup>8</sup> expressed his own belief and that of many others that bacterial toxins in general were the cause. The toxin theory receives especial emphasis in those cases in which it is not possible to cultivate organisms from the lymph gland tissue, and, because in many of the latter instances bacteria can be cultivated in more or less abundance from a demonstrable lesion in the associated and related part of the alimentary canal, it seems impossible to some to avoid the conclusion that bacteria-produced toxins are the cause of the lymph node enlargement. The assumed mechanism is that of an acute lymphangitis in general. In the intestine and mesenteric gland cases visualization of any such lesion is, however, not possible, except at post-mortem examination.

It seems impossible to me, however, to avoid the assumption that ordinarily there can be no pure bacterial toxemic cause for the lymph node enlargement. It seems better to postulate that both bacteria and their developed toxins operate together to produce whatever demonstrable pathology there is.

*Mixed Infections.*—It is practically impossible to have any specific bacterial infection occur in the intestinal wall without having other bacterial groups (colon group, streptococcus group, etc.) or other abetting causal agents added sooner or later. While enlargement of the mesenteric nodes may come about as a result of the infection by an original group or strain of bacteria or possibly by some other causal agent, there is good reason to believe that, sooner or later, added infection by other bacterial groups contributes to the original provocation and either initiates, or more probably, aggravates the lymph node lesion.

#### PORTAL OF ENTRY OF THE CAUSAL AGENT IN THE ALIMENTARY CANAL

A consideration of the matter in the immediately preceding classification cannot help but indicate the dominating importance of the alimentary canal as a portal of entry for the causal agent which provokes acute and chronic mesenteric lymphadenitis. Ordinarily this is facilitated by the occurrence of various forms of chemical, physical, or vascular trauma.

The view that organisms may pass through an intact mucosa (Walsham,<sup>138</sup> Morely,<sup>93</sup> Phillip,<sup>103</sup> Wilensky,<sup>141</sup> and others) has not been generally accepted, but there has been experimental proof (MacFadyen and MacConkey<sup>84</sup> and Bartel<sup>7</sup>) which showed the presence of tubercle bacilli in 25 per cent of a series of nontuberculous cases brought to autopsy in which the lymph nodes appeared normal on gross and histologic examination and in which there were no other demonstrable tuberculous lesions in the body. In addition, any bacteriologist can testify to the comparative ease with which other bacteria, especially of the streptococcus group, can be cultivated from abdominal and other lymph nodes which are without any apparent evidence of disease. In addition, also, I believe that during the process of digestion relatively large numbers of bacteria are absorbed along with the products of digestion.

One of the more important considerations in the area of origin of the path by which infection is introduced into the abdominal lymph nodes and becomes retained there as a subacute long continued process. In my previous communication<sup>14</sup> regarding acute mesenteric lymphadenitis, I discussed this phase of the problem very extensively. The oronasopharyngeal cavity and the terminal part of the ileum are the points of election as portals of entry for the causal agent because of the superabundant content of lymphadenoid tissue and because the mechanism is intimately concerned with the presence of the latter in both of these areas.

*Portal of Entry of the Causal Agent in the Throat.*—The general term throat infection is used to include "that whole group of nonspecific, sporadic, endemic, epidemic, pandemic, febrile infections that have their primary locus in the nose and throat and are variously called tonsillitis, pharyngitis, nasopharyngitis, sore throat, cold, streptococcus throats, rhinitis, laryngitis, bronchitis, upper respiratory tract infection, angina, glandular fever, grip or influenza."<sup>15</sup>

Pediatricians are well acquainted with the fact that during such infections abdominal symptoms of pain, nausea, and vomiting with fever, and other signs of bacterial infection are common (Kleiber,<sup>12</sup> Brennermann,<sup>17</sup> and others). Conversely speaking, observers have noted that frequently abdominal symptoms, for which a mesenteric adenitis has been demonstrably shown to be an accompaniment or sequel, are preceded or even accompanied by some such throat infection. Only in the sense that such infections are prone to more or less frequent repetitions and may therefore lead to advanced incompletely retrogressed pathologic anatomical changes in the lymph nodes may one consider them as chronic conditions.

*Portal of Entry in the Ileum.*—The general anatomical arrangement in the lower ileum is very similar to that in the oronasopharynx. The alimentary canal in either place harbors an extraordinary collection of lymphadenoid tissue (tonsils and adenoids, Peyer's patches) from either of which the lymphatic channels communicate directly with anatomically differentiated groups of lymph glands (cervical glands, mesenteric glands). In either case the functional purpose is also similar and pathologic changes repeat themselves. In the former the association of infection in the lymphadenoid tissue of the oropharynx with secondary cervical adenitis finds similar duplication in the association of lesions of Peyer's patches and other similar intestinal lymphadenoid collections with secondary mesenteric adenitis (e.g., typhoid fever, dysentery, forms of colitis, etc.). The analogy between the oronasopharynx and the lower ileum is most extraordinary.

*Combined or Associated Portal of Entry.*—The upper end of the alimentary canal (ornasopharynx) acts also as a portal of entry for the causal agent in that the latter is swallowed and, passing along the digestive tube, reaches the lower ileum from which and in which it is absorbed.

Various mechanisms of introduction, absorption, and spread of the infection (i.e., causal agent) have been suggested by various observers. A hematogenous method is emphasized by some. Here the presumption is that the organisms penetrate the wall of the alimentary canal and are distributed throughout the body by the blood and form metastatic foci in the intra-abdominal nodes. Upon purely clinical grounds, other observers suggest a simultaneous infection of the entire lymphatic system through purely lymphatic channels in which the abdominal glands take part. Both of these methods do not adequately stress the initial spread by contiguity and the importance of ordinary forms of lymphangitis in what, in my opinion, is the most common mechanism of introduction and spread of the causal agent.

*Intra-abdominal Lymphangitis.*—Our entire conception and assumptions regarding the clinical importance of intra-abdominal lymphangitis and lymphadenitis must be revised. Up to the present these have been accepted too lightly and in an indefinite way and have not been adequately correlated with the observable subjective and objective symptomatology.

Pribram's<sup>108</sup> observations as to lymphangitis in the mesenterium will deserve attention. Pribram (1926)<sup>108</sup> emphasized the occurrence of lymphangitic alterations strongly, and described the appearance of chronic lymphangitis in the mesenterium emanating from insignificant, possibly not even noticeable, inflammatory alterations in the intestinal wall. According to Pribram the altered lymphatic vessels in the mesenterium may be observed as strings, even of the thickness of the radial artery. Pribram<sup>108</sup> considers that the glandular alterations he has observed, now as acute enlargements and now as cicatricial processes with periadenitis, play a less predominant symptomatic role than lymphangitis. Pribram's<sup>108</sup> interpretation has followed the commonly accepted assumption that the appendix was at the bottom of the trouble, but he notes that even after appendicectomy the process showed a tendency to successive spreading and occasional recrudescence, leading to shrinking of the mesenterium and diffuse adhesions in different parts of the abdominal cavity owing to spreading of the infection in the subserous peritoneal lymphatic plexus. The lymphatic vessels of the portal fissure become infected in the same way, resulting in pericholecystitis, periduodenitis, and possibly in a consequent spread of the infection to the pancreas. Pribram<sup>108</sup> attaches great importance to the mesenteric alterations he describes. They are, he thinks, often the cause of discomforts after appendicectomy in cases of chronic appendicitis and are a link with other more or less obscure affections; e.g., pancreatitis and peptic ulcer. Appendicectomy and cholecystectomy respectively at an early stage are recommended also as prophylactic measures.

In spite of the fact that some of Pribram's conclusions are perhaps rather far fetched, his opinion regarding the clinical role and importance of intra-abdominal lymphangitis, and regarding the diagnostic



except in rare instances, the anatomical arrangement was such that it would be impossible for the infection to be transmitted from the appendix to the mesenteric nodes. The exceptions include the rather uncommon anatomical situation in which an abnormal collateral lymphatic anastomosis is present usually through or to the ileocolic chain. In this regard there could be no differentiation between an acute case and a chronic case of lymphadenitis so that we must conclude likewise in the chronic cases that the appendix would not, except uncommonly, directly involve the mesenteric nodes.

A somewhat different situation, however, could very well occur in which a bona fide infection of the appendix could spread by continuity in its immediate environment and for variable distances therefrom through the peritoneal and subperitoneal lymphatics. Evidences of this are constantly available in abdominal explorations (1) in the acute cases as localized or more or less diffuse peritonitides and (2) in the chronic or long-standing cases in the presence of right-sided abdominal adhesions which show every evidence grossly of being centered in the appendix. Any operating surgeon can substantiate these findings. Similar changes occur very often about the gall bladder and sometimes it is difficult to differentiate, when the area of adhesion is large enough to involve both, whether the original point of infection was in the appendix or in the gall bladder.

#### PATHOLOGY OF MESENTERIC LYMPHADENITIS

In interpreting chronic enlargements of the intra-abdominal nodes it is important to be able to judge how much of any enlargement is due to the normal wear and tear of life. Ordinarily, however, I believe this does not play an important role, in spite of Still's<sup>126</sup> post-mortem experience that 59 per cent of routine autopsies made in all sorts of conditions in children showed various lymphatic gland enlargements. My own operating room experience is not at all in accord with Still's post-mortem experience, except in the presence of definitely specific forms of disease.

In the acute cases intra-abdominal lymphadenopathy occurs (1) as part of a generalized adenopathy, (2) as an initial involvement of one group of glands with spread to other groups, and (3) as limited to one anatomically differentiated group of glands. Even though chronic lymphadenopathies may begin in any of these ways, the rule is to find only one group of glands involved, although exceptions occasionally occur.

The observed lesion in simple mesenteric adenitis usually shows nothing indicative beyond a simple hyperplasia confirming the fact that all parts of the glands are in active reaction to whatever the cause of the inflammation and swelling may have been. This is the usual lesion. In old cases some connective changes occur. More differentiated pictures have also been described.

Hadfield's<sup>52</sup> case, in which chronically inflamed glands were present in association with a granulomatous intestinal lesion, presented a clear-cut specific formation of giant-cell systems identical with that found in the thickened submucosa. Some of the sections showed as many as twenty to thirty foci of noncaseating giant-cell systems, while other glands did not show any, and, as the lesions grew older, these giant-cell systems were more and more difficult to find and were replaced by a picture of a simple nonspecific lymphadenitis.

Pratt's<sup>106</sup> observations in the case of the same patient with mononucleosis both during an acute stage and in a later chronic stage showed the usual forms of hyperplasia, early degenerative changes in the vessel walls with hemorrhage, and marked reticuloendothelial proliferation with some necrosis. Longcope<sup>82</sup> noted the occasional presence of large epithelioid cells.

In acute cases similar observations were made in a case of iodism (Barker and Wood<sup>6</sup>) and in scarlet fever (Schlegel<sup>120</sup>).

Such giant-cell systems or epithelioid cells approach and are frequently indistinguishable from those of tuberculosis, but the tendency to retrogress without excessive scarring, and the absence of caseation and acid-fast bacilli in them, contradicted this. They are usually found associated with severe infection of the alimentary canal accompanied by necrosis. Whether this peculiar anatomical picture in the lymph nodes has something to do with the intensity of the process in the corresponding part of the alimentary canal is something which, for the present, must be assumed. Inasmuch as in the very much milder form of nonspecific adenitis only a hyperplastic condition is present in the lymph nodes, indicating a correspondence of intensity of process between the lymph node picture and the picture in the intestinal tract, it must be assumed that the differences in the anatomical picture are caused by the different gradations of toxicity of the etiological cause or of the size and intensity of the dose of the causal agent which is delivered.

We must also assume that the so-called tubercle arrangement can be found not only in specific forms of infection like tuberculosis and syphilis, but also in forms of nonspecific infection in which up to the present time no definite cause can be assigned. It might very well be that this sort of picture represents the anatomical progression between simple forms of lymphadenopathy on one hand and those of definitely specific anatomical pictures, which are customarily correlated less often with syphilis and especially with tuberculosis. Undoubtedly this also explains the confusion which occurred, not only in the earliest historical period of this subject, but even as well in later times in classifying all forms of enlargement of the mesenteric glands as tuberculous.

Mixed infection in tuberculous adenitis plays a very important role. It is commonly noted in the neck. Less frequently it is observed clinically in the abdomen.

Head<sup>55</sup> reported a case of tuberculous mesenteric lymphadenitis in which secondary infection and rupture occurred. He found two similar cases reported in the literature.

Undoubtedly there must be many other similar cases in the available experience. In such mixed infections the anatomical picture sometimes is vague enough to make it difficult to say definitely whether the infection is originally tuberculous, even though from clinical experience we may feel fairly sure that it is. Mixed infection of tuberculous glands is commonly severe enough to cause sufficient destruction to wipe out a good deal of the glandular structure so that the original tuberculous formation cannot be visualized. Again I should like to point out the similarity between the comparable cases occurring in the cervical region and in the mesenteric area.

#### COMPLICATIONS

The glands become involved even to the point of abscess formation or they continue to be enlarged for a time after the intestinal lesion is healed. This is exactly analogous to what happens in the secondary adenitis of the cervical and retropharyngeal lymph glands following a throat or postnasal infection. Such glands could explain the recurrent pain in the abdomen.

The following complications have been reported:

1. Massive invasion of the entire mesenteric lymphatic gland system.
2. Suppurative periadenitis followed by an infiltration of the mesentery or mesoappendix. In these cases the mesentery becomes markedly thickened.

Moore<sup>92</sup> reports the following case:

A 42-year-old woman was sick for two weeks with "appendicitis," with chills, high fever and sweats, abdominal distention and moderate tenderness. No mass was palpable. At operation the appendix and the pelvic organs appeared normal. To the left of the spine a fluctuating mass was present between the folds of the mesentery, which was taken to be of glandular origin. Drainage was established. Death occurred a few days after operation. The origin of the infection was not determined.

3. Formation of a tumorlike mass situated usually in the ileocecal recess or at the root of the mesentery.

The following notes are from my own experience:

A young man, 23 years of age, was explored for an acute abdominal episode which before operation was taken to be acute appendicitis. The appendix was apparently normal, but the glands in the ileocecal angle were all enlarged. An uneventful convalescence and recovery followed. About one year later the man developed signs of an acute intestinal obstruction and an indefinite mass could be felt in the right iliac fossa directly behind the scar of the previous operation. During the exploration the cause of the obstruction was found to be a large

inflammatory mass in the angle of junction of the ascending colon and the small intestine containing a small focus of suppuration. The coils of the intestine were all matted together. It was not possible to do anything except to drain the abscess and to establish an enterostomy on the proximal side of the mass. The patient died, however, about twenty-four hours later from a diffuse peritonitis.

4. The acute process sometimes results in the perforation and rupture of a suppurating gland (Floderus,<sup>40</sup> Eden,<sup>36</sup> Iselin,<sup>66</sup> Head,<sup>55</sup> Bagg,<sup>5</sup> Bell,<sup>8</sup> and Grimm<sup>50</sup>); an intra-abdominal abscess then results (Eden,<sup>36</sup> Iselin,<sup>66</sup> Head,<sup>55</sup> and Bagg<sup>5</sup>).

Head's<sup>55</sup> patient was a 20-year-old male who sustained an acute abdominal episode with no evidence of any illness during the preceding ten years. There was no demonstrable evidence of tuberculous infection anywhere in the body. At operation a group of enlarged caseocalcareous glands was found at the root of the mesentery with rupture of the largest gland which was as big as a hen's egg. Recovery followed. The pathologic picture was reported as caseocalcareous tuberculous adenitis but this was not supported by finding tubercle bacilli.

Between five and seven months later there were three attacks of acute ileus with spontaneous recovery.

5. Erosive bleeding from large intra-abdominal vessels (Whitworth,<sup>140</sup> Ruescher,<sup>117</sup> Rawitzkaja,<sup>110</sup> and Fischmann<sup>39</sup>).

Fischmann's<sup>39</sup> case was a male 25 years of age who gave a thirty-six-hour history of acute intense abdominal pain with vomiting. Examination showed a tender rigid belly with nothing palpable abdominally or by rectum. An operation was done following the diagnosis of acute appendicitis. The exploration showed a large intra-abdominal hemorrhage coming from a large mass involving the wall of the ileum with infiltration of the mesentery and with perforation and bleeding from a branch of the iliac artery. The specimen was reported as "nonspecific" inflammation.

Material obtained at the post-mortem examination showed an anatomical picture which was not characteristic of tuberculosis and the rest of the body showed no tuberculous foci. Nevertheless, for some unexplained reason, the lesion was assumed to be tuberculous; but in view of the report on the operative specimen and of the other findings, I do not believe this should be accepted.

Whitworth's<sup>140</sup> patient was an imbecile, a 7-year-old male of the tuberculous type. There was a purulent discharge from one ear. There was a long history of colicky abdominal pain. After admission to the hospital, because of the poor general condition, a supportive form of treatment was instituted for three days. Then there was a sudden undiagnosed acute abdominal episode followed very quickly by collapse and death.

The post-mortem examination showed a large quantity of clear fluid in the abdomen. There was some old blood clot and a large amount of new blood clot. There was an area of localized peritonitis around the group of enlarged mesenteric glands, some of which were hard and caseous and some of which were breaking down. The ulceration had spread into the mesentery and eroded a large branch of the superior mesenteric artery. There was no demonstrable bowel lesion and no mention was made of a tuberculous focus elsewhere in the body. Except for the anatomical picture there was no other proof for the assumption of the tuberculous nature of the lesion.

## 6. Vascular thrombosis.

Murray's<sup>95</sup> case was a female 14½ years of age who had complained of lower abdominal pain with vomiting for a few years. Then an acute markedly painful abdominal episode occurred and the physical examination showed a median sub-umbilical mass apparently arising from the pelvis. The rectal and vaginal examinations were negative except that the lower end of the mass was palpable. A diagnosis of hematometra was made. After a short remission of the symptoms there was a recurrence of the pain and collapse.

Abdominal exploration showed a mass the size of a hen's egg which was taken to be a caseating tuberculous gland. This was attached to a bluish discolored bowel and mesentery about two feet from the ileocolic junction. The small intestine was definitely infarcted. Death followed. The post-mortem examination showed a well-marked thrombosis of a group of branches of the inferior mesenteric artery and vein. Except for the anatomical picture, no definite proof was furnished of the tuberculous nature of the condition which it was assumed to be.

7. Compression of the pylorus or duodenum (Floderus,<sup>40</sup> Keppler and Erkes,<sup>71</sup> Matyas,<sup>87</sup> Orth,<sup>100</sup> and Wantoch<sup>139</sup>).

8. Intestinal obstruction (Floderus,<sup>40</sup> Jones,<sup>68</sup> Brüning,<sup>20</sup> Homuth,<sup>61</sup> Wakely,<sup>136</sup> Head,<sup>55</sup> Gutzeit,<sup>51</sup> Koschucharoff,<sup>76</sup> Hubrich,<sup>62</sup> and Mischel<sup>91</sup>). The intestinal obstruction occurs either by pressure of a sizable mass, by angulation due to adhesions, or by some form of local peritonitis.

Wakely's<sup>136</sup> patient was a male 54 years of age who complained of the presence of an abdominal mass, dysphagia, and loss of weight. The abdominal exploration showed a calcareous mass three inches in diameter behind the branches of the superior mesenteric artery. It was taken to be a completely calcareous gland. No mention was made of tuberculous or any other etiology.

9. Obstruction of the biliary ducts (Floderus<sup>40</sup> and Jean<sup>67</sup>), and obstruction of the portal vein with associated ascites (Floderus<sup>40</sup>).

Jean's<sup>67</sup> case was a female 31 years of age who for ten years had had right hypochondriac pain and who since she had been 1½ months of age had had acute attacks of colic with jaundice. The x-ray examination showed small calculi in a nonadherent gall bladder. The abdominal exploration showed a large gland in the hepatoduodenal ligament compressing the common bile duct. The papilla and pancreas were negative. The gland was enucleated and a cholecystectomy done and a cure followed. The histology of the gland showed an inflammatory lesion.

10. Calcification of nodes overlying the ureters may result in compression of the ureter with symptoms of disease of the urinary tract such as hematuria, frequent and painful micturition, abdominal pain simulating ureteral colic (Schmieden,<sup>121</sup> Walker,<sup>137</sup> Davidovitch,<sup>31</sup> and Golden and Reeves<sup>47</sup>), and hydronephrosis (Hepburn<sup>57</sup> and Valentin<sup>132</sup>).

## RELATIONSHIP OF CHRONIC INFLAMMATORY ENLARGEMENT TO TUBERCULOSIS OF THE INTRA-ABDOMINAL NODES

In many of these patients there is a history of heavy exposure to tuberculosis in childhood but at the time of examination evidences

of tuberculosis are not obtainable either by physical examination or by laboratory tests. In girls there is sometimes more than the usual rise in temperature at the time of menstruation.

Physical examination generally shows a thin, nervous young woman with a temperature around 100° F. or less, and a tender abdomen. Sometimes an appendicectomy has already been done or at other times is presented as the question at issue. Roentgenographic evidence of disease of the stomach, gall bladder, and colon will not show anything abnormal, but occasionally calcified intra-abdominal lymph nodes are visualized.

The observations upon the occurrence of tuberculous mesenteric lymphadenitis were first performed upon autopsy material, then based upon clinical cases, and finally, much has been learned by direct observations during surgical operations. It appears that in general clinical experience tuberculous infection of the mesenteric nodes is relatively and actually infrequent as an independent lesion and varies from 1 to 3 per cent (Osler and McCrae<sup>101</sup>). However, when it is taken in conjunction with other tuberculous foci in the body, the frequency of mesenteric node infection was noted to reach as high as 79 per cent (Rilliet and Barthéz,<sup>113</sup> Woodhead,<sup>143</sup> Colman,<sup>26</sup> Carr,<sup>21</sup> Branson,<sup>16</sup> Fordyce,<sup>41</sup> Still,<sup>126</sup> Haman,<sup>53</sup> and Conrath<sup>28</sup>). Taken in association with gastrointestinal tuberculosis, the frequency runs somewhat less, about 68 per cent.

Data based upon surgical investigation have been reported from many sources, but a good part of the literature, as is to be expected, consists of isolated case reports. Nevertheless, the following series are available (Table I).

TABLE I

	NO. OF CASES OBSERVED	DURATION OF STUDY IN YEARS
Mächtle (1908) <sup>85</sup>	14	
Floderus (1912) <sup>40</sup>	18	10
Risely (1915) <sup>114</sup>	30	
Carson (1919) <sup>22</sup>	50	8
Mettenleiter (1926) <sup>90</sup>	29	10
Ljunggren <sup>81</sup>	60	4
Bagg (1927) <sup>5</sup>	30	8

In 1926 Braithwaite<sup>15</sup> could find an incidence of only 0.74 per cent of 58,731 laparotomies in which evidence of tuberculous infection of the mesenteric lymph glands was present. Geographic considerations apparently play some role in the determination of the reported figures.

Although tuberculosis of the appendix occurs in about 2 to 5 per cent of pathologic appendices (Lennander and Nyström<sup>79</sup>), no case clearly associated with enlargement of the mesenteric nodes has been recorded (Mead<sup>59</sup>). The similarity of the symptoms present in cases clinically

## 6. Vascular thrombosis.

Murray's<sup>95</sup> case was a female 14½ years of age who had complained of lower abdominal pain with vomiting for a few years. Then an acute markedly painful abdominal episode occurred and the physical examination showed a median sub-umbilical mass apparently arising from the pelvis. The rectal and vaginal examinations were negative except that the lower end of the mass was palpable. A diagnosis of hematometra was made. After a short remission of the symptoms there was a recurrence of the pain and collapse.

Abdominal exploration showed a mass the size of a hen's egg which was taken to be a cascating tuberculous gland. This was attached to a bluish discolored bowel and mesentery about two feet from the ileocolic junction. The small intestine was definitely infarcted. Death followed. The post-mortem examination showed a well-marked thrombosis of a group of branches of the inferior mesenteric artery and vein. Except for the anatomical picture, no definite proof was furnished of the tuberculous nature of the condition which it was assumed to be.

7. Compression of the pylorus or duodenum (Floderus,<sup>40</sup> Keppler and Erkes,<sup>71</sup> Matyas,<sup>87</sup> Orth,<sup>100</sup> and Wantoch<sup>139</sup>).

8. Intestinal obstruction (Floderus,<sup>40</sup> Jones,<sup>65</sup> Brünig,<sup>20</sup> Homuth,<sup>61</sup> Wakely,<sup>136</sup> Head,<sup>55</sup> Gutzeit,<sup>51</sup> Kosehucharoff,<sup>76</sup> Hubrich,<sup>62</sup> and Mischel<sup>91</sup>). The intestinal obstruction occurs either by pressure of a sizable mass, by angulation due to adhesions, or by some form of local peritonitis.

Wakely's<sup>136</sup> patient was a male 54 years of age who complained of the presence of an abdominal mass, dysphagia, and loss of weight. The abdominal exploration showed a calcareous mass three inches in diameter behind the branches of the superior mesenteric artery. It was taken to be a completely calcareous gland. No mention was made of tuberculous or any other etiology.

9. Obstruction of the biliary ducts (Floderus<sup>40</sup> and Jean<sup>67</sup>), and obstruction of the portal vein with associated ascites (Floderus<sup>40</sup>).

Jean's<sup>67</sup> case was a female 31 years of age who for ten years had had right hypochondriac pain and who since she had been 1½ months of age had had acute attacks of colic with jaundice. The x-ray examination showed small calculi in a nonadherent gall bladder. The abdominal exploration showed a large gland in the hepatoduodenal ligament compressing the common bile duct. The papilla and pancreas were negative. The gland was enucleated and a cholecystectomy done and a cure followed. The histology of the gland showed an inflammatory lesion.

10. Calcification of nodes overlying the ureters may result in compression of the ureter with symptoms of disease of the urinary tract such as hematuria, frequent and painful micturition, abdominal pain simulating ureteral colic (Schmieden,<sup>121</sup> Walker,<sup>137</sup> Davidovitch,<sup>31</sup> and Golden and Reeves<sup>47</sup>), and hydronephrosis (Hepburn<sup>57</sup> and Valentin<sup>132</sup>).

### RELATIONSHIP OF CHRONIC INFLAMMATORY ENLARGEMENT TO TUBERCULOSIS OF THE INTRA-ABDOMINAL NODES

In many of these patients there is a history of heavy exposure to tuberculous in childhood but at the time of examination evidences

Dunham<sup>33</sup> found calcified mesenteric nodes in 11 per cent of 1,152 children examined routinely. Dunham and Smythe (New Haven)<sup>33</sup> found that 17 per cent of 120 children with positive tuberculin tests had x-ray evidence of calcified mesenteric glands.

Schechter<sup>119</sup> found an incidence of 1.9 per cent in routine orthopedic studies and 2.8 per cent in routine urological studies.

The following autopsy experience was reviewed by Golden and Reeves:<sup>47</sup>

Opie (St. Louis)<sup>99</sup> was unable to find a single case in routine autopsies made upon 93 children and 50 adults. Hof (Kiel)<sup>59</sup> found tuberculous mesenteric glands post mortem in 1.4 per cent of 7,203 children and 0.8 per cent of 7,683 adults without evidence of tuberculosis elsewhere in the body. Bietzke<sup>11</sup> (Berlin Pathological Institute) similarly found a frequency of 0.9 per cent in 1,100 autopsies.

Schechter's<sup>119</sup> conclusions seem well founded, that the relation of the symptoms to these demonstrable calcified lymph nodes is not well established.

Many an anatomical diagnosis of tuberculous mesenteric adenitis has been and continues to be made upon the roentgenographic demonstration of calcifications in the general region of the lower right abdominal quadrant. According to Kleiber<sup>72</sup> and Strömbeck (Berlin Clinic),<sup>127</sup> however, Pribram<sup>108</sup> was of the opinion that glandular calcifications might set in as a final stage of any pathological process without there having preceded any infection with tubercle bacilli. Noeske<sup>97</sup> had also subscribed to the same opinion. In the former case, none of the observers had any method of reliable proof except for the demonstration of the presence of tubercle bacilli which was frequently not available. In the latter group the contrariwise opinion was held because tubercle bacilli were not demonstrated and because of other clinical and collateral knowledge.

That inflamed and enlarged mesenteric and retroperitoneal glands, nontuberculous in origin, do occur is well known. In his recent paper on abdominal pain in children, Hutchison<sup>64</sup> emphasizes the importance of enlarged glands in the causation of abdominal pain in children.

I, personally, am convinced from all of my experience that, although tuberculous infection is well known and has been adequately proved to exist in the mesenteric and other abdominal lymph nodes, there are also other cases of chronic inflammatory enlargement of these nodes with and without necrosis and with or without calcification which are not caused by infection with the tubercle bacillus.

A good many of these roentgenographically demonstrated calcifications are not expected findings and Schechter's<sup>119</sup> conclusions should be kept in mind because of their fundamental truth:

"A large percentage of the cases, 80 per cent in this series, revealed either absence of abdominal pain and tenderness or localization of these

recognized as tuberculous adenitis to that of appendicitis has been commented upon by many other observers including Franke (1914),<sup>43</sup> Clute (1920),<sup>25</sup> Struthers (1921),<sup>128</sup> Krogsgaard (1922),<sup>77</sup> Freeman (1923),<sup>44</sup> Braithwaite (1926),<sup>15</sup> Klein (1926),<sup>73</sup> Ljunggren (1926),<sup>61</sup> Mettenleiter (1926),<sup>90</sup> Wilensky and Hahn (1926),<sup>141</sup> Bell (1927),<sup>8</sup> Bagg (1927),<sup>5</sup> McFadden (1927),<sup>88</sup> Rendle Short (1928),<sup>112</sup> Strömbeck (1932),<sup>127</sup> and others.

In going through the literature one notes almost immediately, especially in earlier communications, that there has been a considerable amount of loose thinking and that a great many of the assumptions of the presence of tuberculous infection are not supported by sufficiently adequate laboratory confirmation. In the very excellent report made by Strömbeck<sup>127</sup> he makes the statement that it is "partly by elimination" that the diagnosis of tuberculosis is accepted. In addition it is highly significant that of the 37 cases reported by Foster in which a clinical diagnosis of tuberculous mesenteric adenitis was made microscopic proof was available for only 4, or 10 per cent.

One of Strömbeck's<sup>127</sup> cases showed one of the bizarre conditions which are sometimes encountered and the difficulties of interpretation. The following case, the notes of which are herewith given, is listed by Strömbeck<sup>127</sup> among his cases of tuberculous mesenteric lymphadenitis.

Since the age of 10 years, a patient 16 years of age complained of abdominal pain after meals lasting for from ten to fifteen minutes. The patient was always well nourished. During the preceding six months, however, there had been poor appetite and the patient looked tired and pale.

During the preceding fortnight, gradually increasing meteoristic pains in the pit of the stomach appeared and, at the time of admission to the hospital, a distinctly tender mass the size of a walnut was palpable to the right of the umbilicus. The spleen was not palpable. The laboratory examination showed a positive agglutination for paratyphoid B, 1-1280, and *B. paratyphosus* was cultivated from the stools. The x-ray examination demonstrated the presence of a calcific intra-abdominal mass which was taken to be a calcareous gland.

After several months the patient became symptom-free and the stool culture finally became negative.

It is quite apparent that the question of tuberculous infection as an etiological factor for the symptoms is considerably in doubt.

Since the development of roentgenography, much emphasis has been put upon the visual demonstration of calcified areas which, when present in the right lower or mesial parts of the abdominal cavity, have been routinely assumed to be calcified lymph nodes. A review of the experiences of several observers along these lines made by Schechter<sup>119</sup> showed the following:

Strömbeck (Stockholm)<sup>127</sup> found calcified mesenteric nodes in 7 to 8 per cent of the x-ray plates made upon 600 patients examined for various miscellaneous abdominal symptoms.

abdominal symptomatologies which have previously not been correctly integrated. Further spread of the lymphangitic process leads to the associated anatomically related lymph glands in the mesentery in which the first and usually successful attempt is made to block the spread of the pathologic process.

The anatomical characteristics of chronic nonspecific mesenteric adenitis is frequently superficially similar to that of tuberculous infection, but in these more or less doubtful cases, it is rarely possible to prove the contention by the demonstration of tubercle bacilli in the tissue sections. Because of this many of the assumptions made in the early and previous reports must be considered not proved. The presence of calcifications in these nodes in view of newer knowledge must not be considered as being automatically indicative of a tuberculous infection. And it seems certain now that many of these chronic inflammatory glandular enlargements do not result from an infection with tubercle bacilli.

There is a marked and striking resemblance between intra-abdominal glandular enlargements (chronic mesenteric adenitis) and similar glandular enlargements in the neck (chronic cervical adenitis) in all its phases: causal, etiological, anatomical, clinical, etc.

In mesenteric adenitis the diverse character of the symptomatology and the extensive mimicry of other definitely correlated symptom complexes are easily understandable and are due no doubt to the fact that no single cause accounts for the lymph gland enlargement. The protean character of the symptomatology simply reflects the original primary area in which the infection occurred or a secondary area in which some complication has taken place.

#### TREATMENT

Inasmuch as in many cases abdominal lymphadenopathy is part and parcel of some larger definite clinical entity, treatment must follow along the lines known by experience to be correct and adequate for the original disease. In nonspecific mesenteric adenitis and in the absence of any suppuration or other complication, none but conservative treatment would be indicated; and, for the obvious reasons, the therapy must imitate to a large extent that which is customary for any chronic illness and even that for tuberculous infection; i.e., improvement in nutrition, rest, attention to any anemia, heliotherapy, etc. Anorexia and vomiting are particularly difficult to handle and indicate overfeeding. Sedatives should be employed as indicated.

Conservative treatment is excellent provided that one could so perfectly diagnose the condition that the fear of an undiscovered surgical condition and/or emergency could be definitely eliminated. Unfortunately this is not possible at the present writing in clinical practice and abdominal explorations are more or less frequently necessary in order to establish the true nature of the intra-abdominal condition.

symptoms at sites other than that of the calcified nodes. Of this number, 28.5 per cent had no abdominal pain or tenderness.

"Abdominal pain and tenderness, which are considered outstanding symptoms in the clinical evidence of calcified mesenteric lymph nodes, do not appear to bear this symptom relationship when these nodes are found in routine roentgen studies of the gastro-intestinal tract. The relationship to the general symptoms of nausea and vomiting is also indefinite."

The conclusions of Golden and Reeves<sup>47</sup> based upon observations in seven cases do not agree with those of Schechter.<sup>119</sup> The explanation undoubtedly lies in the fact that the cases of the first group were in a stage of acute exacerbation, while those of Schechter were in a quiescent period; i.e., chronic.\*

#### SUMMARY AND CONCLUSIONS

Chronic simple nonspecific intra-abdominal mesenteric adenitis is either a continuation of an incompletely resolved acute episode, or results from a succession of acute episodes, each of which is probably an exacerbation of an underlying persistent infection or a long drawn-out continuous process. In any event, its etiology and pathogenetic mechanism originally are essentially similar to those of acute mesenteric adenitis.

The portal of entry for the infection is the alimentary tract and the solitary and, especially, the aggregated follicles of lymphadenoid tissue have much importance as being the most common specific areas through which the causal agent enters. The appendix usually does not act as a portal of entry for the infection except in comparatively rare instances, and this is only possible in the presence of certain anatomical abnormalities.

The most commonly found causal agent is some strain of the streptococcus group. Some observers have attempted to correlate some unusual groups of organisms, such as the brucellosis or tularensis groups, but these suggestions or assumptions have not as yet been substantiated. It seems that parasitic infection is more apt to be associated with chronic lymphadenopathy than with its acute form. A suggestion made by some that intestinal stasis is the forerunner of similar lymphadenopathy is probably only true in the sense that it facilitates a state of chronic infection of the lymphatics and mesenteric glands. In any event mixed infections are necessarily common.

The pathologic anatomical process begins at the portal of entry and spreads by contiguity in the anatomically related lymph channels as a true lymphangitis. The importance of the latter has not hitherto been sufficiently stressed and it is necessary to emphasize the lymphangitic process as an explanation of many acute and/or chronic intra-

\*Compare this with the description of the roentgenographic findings in the previous part of this communication.

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## Book Reviews

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**Diseases Affecting the Vulva.** By Elizabeth Hunt, B.A., M.D., Ch.B. Cloth, Pp. 207, with 36 illustrations and 18 color plates. The C. V. Mosby Co., St. Louis, 1940. \$4.50.

As the vulva is composed of stratified squamous epithelium, the gynecologist or practitioner should not lose sight of the fact that it is subject to the same lesions that may affect this type of integument elsewhere in the body. Since the author of this volume is a dermatologist, it naturally contains much valuable information not ordinarily found in standard texts on gynecology.

The material, which includes all lesions from the most common to the rarest, is presented in a clear and concise manner and is considerably enhanced by thirty-six illustrations and eighteen plates in color. The latter are marvelous examples of photographic art, clearly depicting the vulval lesions and in themselves forming a valuable addition to any gynecologist's library.

This volume of two hundred and seven pages is enthusiastically recommended to the gynecologist, dermatologist, and practitioner.

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**Histopathology of the Peripheral and Central Nervous System.** By George B. Hassin, M.D., Ed. 2. Cloth. Pp. 554, with 302 illustrations. New York, 1940, Paul B. Hoeber Co. \$7.50.

As the title of this book indicates, the author has limited himself almost exclusively to a detailed histologic description of the diseases of the nervous system, excluding almost entirely the gross changes. This immediately limits the usefulness of this work to those specialists who are already somewhat familiar with the microscopic tissue alterations. An attempt has been made to correlate briefly some of the clinical symptoms with the pathologic changes. The author devotes some space to discussions of the various theories of the pathogenesis of some of the central nervous system lesions. In discussing these theories he frequently dwells upon his own rather than upon the more commonly accepted ones. This is best illustrated in the discussion of the secretion and formation of spinal fluid.

The usual plan is adopted of dividing the nervous system into large divisions, such as the peripheral nerves, cord, and brain, and of describing the pathologic involvements occurring in each system. A fourth section on diseases of the muscles is included. Here one finds a discussion of such conditions as myasthenia gravis and the muscular dystrophies. The grouping of the various disease conditions is not always conventional; for example, Schilder's disease, which is a diffuse type of sclerosing disease, is discussed along with such encephalitic conditions as botulinus, Wernicke's disease, postvaccinal encephalitis, and the like.

Many of the histopathologic descriptions are excellent. Those concerning tabes, poliomyelitis, amyotrophic lateral sclerosis, and general paresis certainly warrant reading by everyone. Certain details included within this book cannot be found in any other single publication on the same subject. The author gives careful descriptions of the brain lesions in such rare conditions as yellow fever, bubonic plague, Borna disease, Rocky Mountain spotted fever and Niemann-Pick disease. The illustrations throughout are very good.

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**Demonstrations of Physical Signs in Clinical Surgery.** By Hamilton Bailey, F.R.C.S. (Eng.). Ed. 7. 377 illustrations. Baltimore, 1940, The Williams and Wilkins Co. \$6.50.

The seventh edition of Bailey's book, like the preceding editions, contains a great deal of practical and useful information. It is profusely illustrated with excellent photographs and diagrams. Some of the illustrations are in color.

This book cannot be considered a satisfactory treatise on the physical diagnosis of surgical conditions for either the student or practitioner. Certain of its defects are obvious. It is far from complete. The value as well as the validity of some of the signs described must be questioned. No consistent attempt has been made to give the pathologic or physiologic mechanism producing the various physical signs which are considered.

Due attention has been paid to tradition by including as footnotes the names and dates of the men who have demonstrated and emphasized the various diagnostic signs. The text is well written and the index adequate.

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**The Physiological Basis of Medical Practice.** By Charles Herbert Best, M.D., and Norman Taylor, M.D. Ed. 2. Pp. 1,872 with 497 illustrations. Baltimore, 1940, The Williams and Wilkins Co. \$10.00.

Pathology has been bound up so intimately with the activities of the surgeon that usually he has neglected physiology to orient himself in the apparently more practical concepts of pathology. Within the last few years, however, the importance of physiology to the practical man of medicine, whether general practitioner, surgeon, or other type of specialist, has become so obvious that this disinterest of the clinician in physiology will not long be palpable. The young surgeon, in particular, has learned that one of the best texts for his hours of study is a comprehensive work on physiology. More and more, too, the aspirant for a career in surgery is becoming alert to the importance of physiology as a proper approach to surgery.

The intention of the authors was to bridge the activities of the laboratory and the clinic in such a manner that the undergraduate student would appreciate the value of physiologic tenets in the treatment of disease. This objective the authors have accomplished in a superb manner. Moreover, they have created an extremely useful sourcebook to which the earnest student of medicine may turn daily for enlightenment concerning normal and disturbed physiologic processes. It is, undoubtedly, one of the best books for general orientation with which a surgeon may provide himself. It can be recommended with enthusiasm to all practitioners of medicine. He who will study it earnestly will become a better and more scientific physician or surgeon.

Some of the best chapters in this book are on the peripheral nerves. Here one finds a most excellent review of their normal structure and their histopathologic alterations. The most disappointing chapter is that on brain tumors. The author apparently has ignored the comprehensive work of Bailey in classifying and simplifying the various types and has adopted the inadequate division of these neoplasms into benign and malignant. He then groups together for description a large number of miscellaneous, unrelated tumor types. Meningiomas are included with the benign tumors in spite of the fact that the mesenchymal, sarcomatous, and melanotic meningiomas are most fulminating, both in their microscopic appearance and clinical course. The slow-growing astrocytoma is classified as malignant. The discussion of the gliomas is brief and unbalanced. For example, only eight lines are devoted to the ependymomas, which comprise about four per cent of the intracranial neoplasms, while over a page is spent in the discussion of the epidermoids which comprise about one-half per cent of the intracranial neoplasms. A very useful bibliography follows each of the chapters. The text is concluded by a fairly convenient section on staining techniques.

This book would make an excellent addition to the library of the specialist in the field of neurology and neuropathology and would be very convenient to have around a neuropathologic laboratory. For others, the style and the detail would make it somewhat difficult to follow.

**Illustrations of Surgical Treatment, Instruments, Appliances.** By Eric L. Farquharson. Pp. 338, with 259 illustrations and 57 plates. Baltimore, 1939, Williams and Wilkins Co. \$6.50.

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While one may not agree with all the methods of treatment (the technique of continuous intravenous infusion is particularly complicated), one must agree that the illustrations are excellent and the description of treatment clear and concise.

The exact need, however, for such a volume is not apparent, as the better textbooks of surgery describe the methods of treatment just as clearly and the catalogues of the larger surgical supply houses illustrate instruments and appliances equally as well. It will probably be of greatest value as a surgical reference book for surgical house officers and nurses unacquainted with various surgical methods and treatments.

**Fractures.** By Paul B. Magnuson. Pp. 511, with 327 illustrations. Philadelphia, 1939, J. B. Lippincott Co.

Into a small volume the author has compressed a great deal of practical information concerning the management of fractures. The book abounds with practical suggestions that will prove helpful to those concerned with fracture management. The illustrations are numerous and of high quality. The author has rightfully stressed anatomical knowledge of muscle action as a necessity in the intelligent reduction of fractures.

A well-chosen bibliography is appended. One legitimate criticism of the monograph would appear to be the rather limited space devoted to the healing process attending breaks in the continuity of bone. Further, failure to discuss pathologic states of bone, such as Paget's disease and hyperparathyroidism, appears to this

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## Original Communications

### THE STATISTICAL METHOD

#### A VITAL TOOL IN CLINICAL MEDICINE

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*(From the Laboratory for Surgical Research, Harvard Medical School)*

CLINICIANS seem to have an innate fear of mathematics. Hence, the statistical method, which could serve them as a valuable tool, is now used for the most part by the research workers and the academic laboratories. Medical journals contain an increasing number of papers based upon mortality and morbidity rates on groups of patients who have received different treatments. The conclusions of most of these papers based upon rates and percentages are worthless.

A statistical analysis of percentages would do much to clarify the present muddled state of the profession regarding the correct treatment of many common maladies. It is common at medical meetings to observe doctors presenting figures showing that a certain procedure in the hands of one has been attended by a decreased mortality; in the hands of the other, by a heightened mortality. Each implies that the other is a prejudiced observer (or worse); each maintains that the percentages derived from his series are conclusive. More often than not, each protagonist bases his contention on mere chance variation; had either or both been aware of the rudiments of the statistical approach, there would have been no controversy.

The following, although hypothetical, is typical of statements in clinical literature: "In the series with delayed operation the mortality was 1.5 per cent, whereas in the series with immediate operation the mortality was 4.8 per cent. Thus it is seen that death occurs more than three times as frequently after immediate operation." It is true that 4.8 is more than three times 1.5; however, from the standpoint of recovery there is little difference between 95.2 per cent and 98.5 per cent. Any two therapeutic procedures which result in recovery so frequently cannot be very different. The differences between 1.5 and 4.8 per cent and

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## Books Received

The receipt of books is acknowledged in this section and this statement must be regarded as sufficient acknowledgment of the courtesy of the senders. Selections will be made for more extensive review dictated by the interests of our readers and as space permits.

**THE SURGICAL CLINICS OF NORTH AMERICA**, Vol. 21, Chicago Number (February, 1941). By many authors. Cloth. Pp. 309, with 101 illustrations. Philadelphia, 1941, W. B. Saunders Co.

**OBESITY AND LEANNESS**. By Hugo R. Rony, M.D., formerly Associate in Medicine and Chief of Endocrine Clinic, Northwestern University School of Medicine, Chicago; formerly Attending Physician, Cook County Hospital, Chicago. Cloth. Pp. 300, with 32 illustrations. Philadelphia, 1940, Lea and Febiger.

**SPERMATOZOA AND STERILITY (A Clinical Manual)**. By Abner I. Weisman, M.D., Adjunct Gynecologist, Jewish Memorial Hospital; Clinical Assistant, Visiting Gynecologist and Obstetrician, Metropolitan Hospital, New York City. Cloth. Price \$5.50. Pp. 314, with 77 illustrations. New York, 1941, Paul B. Hoeber, Inc.

**ANATOMICAL STUDIES ON THE MOTION OF THE HEART AND BLOOD**. By William Harvey, M.D. (A Modern English Translation With Annotations. By Chauncey D. Leake, Professor of Pharmacology, University of California.) Paper. Price \$1.50. Pp. 150, with 9 illustrations. Baltimore, 1941, Charles C Thomas, Publisher.

**CYCLOPROPANE ANESTHESIA**. By Benjamin Howard Robbins, B.A., M.S., M.D., Associate Professor of Pharmacology, Vanderbilt University School of Medicine. Cloth. Price \$3.00. Pp. 175, with 40 illustrations. Baltimore, 1940, Williams & Wilkins Co.

**EMERGENCY SURGERY**. By Hamilton Bailey, F.R.C.S. (Eng.), Surgeon, Royal North Hospital; External Examiner in Surgery, University of Bristol. Cloth. Price \$15.00. Pp. 944, with 930 illustrations. Baltimore, 1940, Williams & Wilkins Co.

**CLINICAL UROLOGY (Vols. I and II)**. By Oswald Swinney Lowsley, A.B., M.D., F.A.C.S., Director of Department of Urology, New York Hospital; and Thomas Joseph Kirwin, M.A., M.S., M.D., F.A.C.S., Attending Surgeon, Department of Urology, New York Hospital. Cloth. Price \$10.00 per set. Vol. I: Pp. 898, with 220 illustrations; Vol. II: Pp. 1,684, with 365 illustrations. Baltimore, 1940, Williams & Wilkins Co.

**HAEMORRHOIDS AND THEIR TREATMENT (The Varicose Syndrome of the Rectum)**. By Kasper Blond, M.D., Formerly Assistant, Rothschild Hospital, Vienna; Hon. Consulting Surgeon, Municipal Hospital, Vienna. Translated by E. Stanley Lee, M.S., F.R.C.S., Hon. Assistant Surgeon, Westminster Hospital. Cloth. Price \$4.50. Pp. 140, with 49 illustrations. Baltimore, 1940, Williams & Wilkins Co.

**SURGERY OF THE HAND**. By R. M. Handfield-Jones, M.C., M.S., F.R.C.S., Surgeon to Outpatients, St. Mary's Hospital; Senior Surgeon, Florence Nightingale Hospital; Examiner in Surgery, University of Cambridge; Society of Apothecaries. Cloth. Price \$4.50. Pp. 140, with 95 illustrations. Baltimore, 1940, William Wood & Co.

**SURGICAL ANATOMY OF THE HEAD AND NECK**, ed. 2. By John Finch Barnhill, M.D., F.A.C.S., LL.D., formerly Professor of Otolaryngology in the Indiana University; Hon. Professor Anatomy, University of Southern California School of Medicine; and William J. Mellinger, M.D., Associate Professor of Anatomy, University of Southern California School of Medicine. Cloth. Price \$15.00. Pp. 773, with 431 illustrations. Baltimore, 1940, William Wood & Co.

Thus we may say,

Error varies with percentage  $\times$  (100-percentage).

Then if we combine these two notions of error, we find, with corrections, that

Error varies with  $\frac{\text{Percentage} \times (100 - \text{Percentage})}{n}$

It can be proved that the error varies as the square root of these factors. If a series becomes ten times as long, the error is not decimated but is decreased only to  $\sqrt{\frac{1}{10}}$  of its previous value. Hence the formula becomes for a given Percentage A,

$$\begin{aligned} \text{Standard Error (S.E.)} &= \sqrt{\frac{\text{Percentage A} \times (100 - \text{Percentage A})}{\text{No. of cases in the series}}} \\ &= \sqrt{\frac{A \times (100 - A)}{n}} \end{aligned}$$

We are now in a position to consider critically the hypothetical statement regarding the merits of early and delayed operation. It is seen that the length of the series is completely ignored. The raw percentages, unmodified by length of series, are used to draw a sweeping conclusion. The other factor, the size of the percentages, is likewise ignored. For convenience in computation let us assume that each percentage was based upon a series of 100 operations. Then in the case of delayed operation

$$\text{S.E.} = \sqrt{\frac{1.5 \times (100 - 1.5)}{100}} = \sqrt{\frac{1.5 \times 98.5}{100}} = \sqrt{\frac{147.75}{100}} = \sqrt{1.4775} = 1.21,$$

and in the case of immediate operation

$$\text{S.E.} = \sqrt{\frac{4.8 \times (100 - 4.8)}{100}} = \sqrt{\frac{4.8 \times 95.2}{100}} = \sqrt{\frac{456.96}{100}} = \sqrt{4.5696} = 2.13.$$

The respective mortalities, then, are not merely 1.5 and 4.8 per cent, but  $1.5 \pm 1.21$ , and  $4.8 \pm 2.13$  per cent. Thus, in another identical series the chance (derived by a mathematical process we need not consider here, but which may be obtained from any book on statistics) is 1 in 3 that either of the mortality percentages might vary as much as one standard error and 1 in 22 that either might vary as much as twice its standard error. In other words, in another completely similar group of patients, there is a possibility that the mortality percentages might be exactly equal, 2.7 for delayed operation, i.e.,  $1.5 \div 1.2$ , and 2.7 for immediate operation, i.e.,  $4.8 - 2.1$ .

Thus far we have considered the individual percentages and their standard errors; but, if percentages may vary so much, the difference between them will vary likewise. The difference between two percentages has its own standard error derived from the standard errors of the

between 95.2 and 98.5 per cent are the same. The important fact is that the difference is 3.3 per cent, not that 4.8 is three times more than 1.5 per cent.

In recent years increased emphasis upon good hospital records is making a large mass of data available to the profession. At every medical meeting and in every medical journal doctors are constantly trying to draw sound conclusions from these figures. With few exceptions, they do not know how. The profession has failed to equip itself with the knowledge necessary to find the truth buried in its own records.

There is a simple method by which percentages may be analyzed, based upon two factors inherent in every percentage. We shall later consider the derivation of the method, but now we give the rule of thumb by which the doctor may compute the soundness of the conclusions upon the margin of the paper in question. The following is the formula for the "standard error" of the difference between two percentages.

$$\sqrt{\frac{\text{Percentage A} \times (100 - \text{Percentage A})}{\text{No. of cases in Series A}}} \text{ plus } \frac{\text{Percentage B} \times (100 - \text{Percentage B})}{\text{No. of cases in Series B}}$$

If the difference between Percentages A and B is less than twice the figure resulting from the above formula, the difference is not statistically significant and may be considered as due merely to chance.

The steps by which this formula is derived and its practical application may now be described briefly.

There are two factors that govern the reliability of any percentage. First, the reliability of a percentage varies with the length of the series. It may be said to be intuitively obvious that 4 per cent of 1,000 is more reliable than 4 per cent of 50. As a first step in the derivation of our formula we may say that:

$$\begin{array}{c} \text{Reliability increases with length of series,} \\ \text{or} \\ \text{Unreliability (error) decreases with } \frac{1}{\text{length of series.}} \end{array}$$

This is another way of saying that the error will be smaller as the length of the series or number of cases ( $n$ ) is larger.

Second, the man in the street realizes that any percentage in the neighborhood of 50 (50-50) is less reliable than a percentage nearer the extremes of 0 or 100. It is an interesting and useful fact that  $50 \times 50 = 2,500$  and  $1 \times 99 = 99$ . If one multiplies any percentage by its complement, one gets a figure that is larger as one approaches "fifty-fifty."

$$\begin{array}{rcl} 10 \times 90 & = & 900 \\ 20 \times 80 & = & 1,600 \\ 30 \times 70 & = & 2,100 \\ 40 \times 60 & = & 2,400 \\ 50 \times 50 & = & 2,500 \end{array}$$

series of 3.4. Obviously this result has no statistical significance because the quotient ( $4.0 \div 3.4$ ) is only 1.2, far below the minimum of 2.0, and represents odds of only 3 to 1 that the difference did not occur by chance alone. A few months later two prominent American surgeons reported a series of 144 early operations (within seventy-two hours) with a mortality rate of 7.6 per cent and 176 late operations with a mortality rate of 3.4 per cent and concluded that late operation was better. The difference in this series is  $4.2 \pm 2.6$  per cent; the quotient ( $4.2 \div 2.6$ ) is 1.6 and hence the difference cannot be considered as beyond the range of chance variation. Both protagonists are drawing conclusions which are not justified by the series at hand.

Thus far we have considered the application of statistical method to percentages only. Although the percentage, e.g., morbidity or mortality rate, is the device most used by clinicians to draw comparisons in scientific papers, the arithmetic mean, the average, is also frequently used. What has been said of the importance of the statistical method in relation to percentages applies with equal force to the average.

It is obvious that: (1) an average derived from a large number of closely grouped observations is reliable; (2) one derived from a small number of widely dispersed observations is unreliable. The reliability of averages may be reduced to a numerical measurement much the same as in percentages. The "standard deviation" becomes the numerator of our fraction and the square root of the number of cases remains the denominator. I suggest that the reader consult Fortuyn or Hill as to the manner of computation of the standard deviation.

I have tried to emphasize the great importance of statistical method, but this does not constitute the whole picture. Accurate observation and logical reasoning are as important as they ever were. They are even more important, if possible, because, to borrow a chemical phrase, the end point has been so sharpened by the statistical method that errors in observation and reasoning are magnified. Clinical investigation may be said to have passed from the qualitative to the quantitative stage with all the painstaking accuracy that this step implies. The statistical method is not a smoke screen for slovenly work. It will not make answers right if the basic reasoning is wrong. It will not correct errors in observation for it can be applied only after the data are collected. The statistical method is but an extension of reasoning.

An example of failure in this respect is the long-standing controversy concerning early *versus* late operation in acute cholecystitis. Many authors of medical papers attempt to ascertain the effect of one variable while ignoring the presence of another. In the literature on cholecystitis an author may classify a patient who enters the hospital on the fifth day of the disease and has an operation within twenty-four hours as an early operation and the patient who enters within twenty-four hours of the onset and has the operation three days later as a late opera-

percentages themselves. The standard error of the difference between Percentages A and B equals the square root of the sum of the squares of the two standard errors.

$$\text{S.E. diff.} = \sqrt{\text{S.E.}_A^2 + \text{S.E.}_B^2}$$

In our series the difference is 3.3 per cent, and S.E. diff. =

$$\sqrt{1.21^2 + 2.113^2} = \sqrt{1.4775 + 4.5696} = \sqrt{6.0471} = 2.5.$$

The difference actually is  $3.3 \pm 2.5$  per cent.

Statisticians vary as to what is a "significant" difference; i.e., a difference sufficiently great to be due to causes other than chance. The minimum requirement is a difference at least twice its standard error. In other words, the odds must be at least 21 to 1 that the difference did not occur by chance. Some are better satisfied if the difference is three times its standard error. Others compromise on a difference which is 2.5 times its standard error. It depends upon the individual's concept of "certainty." If a difference between percentages is twice its standard error, the odds are 1 to 21 that a difference as large as this could occur simply by chance. To some workers this is "certainty." If the quotient obtained by dividing the difference by its standard error is 2.5, the odds are 1 to 80 and, if the quotient is 3.0, they are 1 to 369. One may take one's choice, but, when the quotient is less than 2, the reality of the difference can be established only by amassing a larger series of cases.

In our hypothetical series the difference is less than twice its standard error. The quotient obtained by dividing the difference by its standard error,  $3.3 \div 2.5$ , is 1.3. Therefore, while the delayed operation may be better, that conclusion is not justified when based on this series. Further study must be made or this series must be combined with similar series from other hospitals. And it is quite possible that the proportions in another hospital would be exactly reversed.

Yet the mortality of immediate operation, in the hypothetical series, was "more than three times the mortality of delayed operation." This type of conclusion which sounds so important is gravely misleading, because it ignores the basic rules for evaluating data accumulated from a small sample in terms of its probable occurrence in the unselected population.

To compute the standard errors of percentages is a simple and absolutely necessary procedure. For example, there recently appeared in an American surgical journal an article in which an internationally known surgeon argued strongly for early operation in acute cholecystitis. His conclusions were based on a series of 97 late operations with 7.2 per cent mortality and 62 early operations with 3.2 per cent mortality. The difference between these percentages is 4.0 with a standard error in this

in the experimental method, but they have thus far neglected to teach them an equally useful approach, the statistical method. Twenty years ago Kilgore saw the problem clearly and urged that statistical method have a place in the medical curriculum. There are signs that the medical schools at long last are about to offer courses in statistics to their students.

Pending that long-delayed day when every doctor shall be aware of the necessity of the statistical method in clinical medicine, much can be done by an enlightened medical editorship. Medical editors should demand that statistical papers be properly analyzed and should refuse publication when the standard deviation or standard error is not included. Medical editors must eliminate or educate uninformed authors and inculcate a statistical *critique* in the medical reader.

#### SUMMARY

1. Clinicians have almost entirely neglected criteria of statistical analysis in their scientific writings.

2. The many contradictory teachings and controversial practices originate in part in this neglect of well-recognized statistical procedure.

3. We have described in detail the derivation and application of the simpler formulas as they relate to percentages.

4. With a little thought every doctor can master this technique and apply it in a very few minutes to medical papers which utilize percentages in their conclusions.

5. As presented now, most case series are too brief for sound conclusions. Publication should be withheld until longer series are amassed.

6. A standard classification in such diseases as are now the center of controversy would enable short series to be combined and allow reliable conclusions to emerge.

7. Medical students should receive formal education in statistical procedure.

8. Medical editors should demand of medical authors that their figures and data be statistically sound.

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tion. It is not surprising that ambiguous conclusions emerge. The only logical method is to divide the cases into three groups: those entering the hospital within twenty-four hours of the onset, those between twenty-four and seventy-two hours of the onset, and those entering after seventy-two hours. Then in each group the effects of early and late operation can be determined.

This necessitates a total series of about 1,000 patients, which is too much to expect of the clinicians today. As it is now, the individual series are too short for sound conclusions and the series of various authors cannot be combined because the methods of tabulation differ. It would be profitable if some authoritative surgical association erected a few rules under which gall bladder and other statistics were assembled. Then by a combination of series, reliable conclusions might be attained. As an example we suggest the following outline for assembling statistics on cholecystitis:

- A. Home treatment, 0-23 hours
  - 1. Operated upon in first 24 hours at hospital
  - 2. Operated upon in second 24 hours at hospital
  - 3. Operated upon in third 24 hours at hospital
  - 4. Operated upon in fourth 24 hours at hospital
  - 5. Operated upon in fifth 24 hours at hospital or thereafter
- B. Home treatment, 24-47 hours  
Same as under A
- C. Home treatment, 48-71 hours  
Same as under A
- D. Home treatment, 72-95 hours  
Same as under A
- E. Home treatment, 96 hours or more  
Same as under A

This may seem at first to be unnecessarily complex, but a moment's reflection will reveal that it is what every clinician would like to do; but, when he assembles his cases, he finds that he does not have sufficient cases to make the population of any one group large enough and so makes his classification coarser.

Thus far the age factor has been completely ignored. The above classifications should be repeated for each ten-year age group. No clear-cut teaching has yet emerged in the literature largely because the age factor has been universally ignored. To my knowledge, no report has yet appeared which yields statistically inpeccable conclusions. But within five years of this date, a clear-cut answer to this problem could be made if twenty outstanding clinics would adopt a standard classification and submit their data to statistical analysis. This is only one of several problems confronting surgeons which require the statistical approach for their solution.

#### THE REMEDY

What are we to do about the statistical approach in medicine? The answer rests with the medical schools, which must train every student in the rudiments of the statistical method. Medical schools train students

in the experimental method, but they have thus far neglected to teach them an equally useful approach, the statistical method. Twenty years ago Kilgore saw the problem clearly and urged that statistical method have a place in the medical curriculum. There are signs that the medical schools at long last are about to offer courses in statistics to their students.

Pending that long-delayed day when every doctor shall be aware of the necessity of the statistical method in clinical medicine, much can be done by an enlightened medical editorship. Medical editors should demand that statistical papers be properly analyzed and should refuse publication when the standard deviation or standard error is not included. Medical editors must eliminate or educate uninformed authors and inculcate a statistical *critique* in the medical reader.

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## A BULLET IN THE HEART FOR TWENTY-THREE YEARS

G. GREY TURNER, LL.D. (HON.), D.CH. (HON.), M.S., F.R.C.S.,  
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"Now, slowly, let us hear what befell afterwards—step by step omitting nothing." Kim.

A GENERAL interest in the fate of foreign bodies and recent publications dealing with their effect when lodged in or about the heart encourage me to report the case of a man who is alive and well and has gone about his daily work for the last twenty-three years with a machine-gun bullet lodged in the wall of the left ventricle.

The patient, an officer, 32 years of age, was admitted to a base hospital under my care in April, 1917. Eighteen days before admission, while in the open, he was struck on the front of the left side of the chest by a bullet from a machine gun at an estimated range of 500 yards. There was a snowstorm at the time, and, though he does not remember exactly what he was doing, he thinks he may have had his left arm held up in front as some protection against the driving snow. There was a through-and-through bullet wound of that arm just above the elbow, and he believes that may have been inflicted by the bullet which penetrated the chest. In its course the missile traversed a service waterproof and the left breast pocket of his tunic and its contents, consisting of a bundle of six letters and a pocketbook one-half inch thick (Fig. 1), at the same time grazing the edge of a wooden ruler and, of course, penetrating his shirt (Fig. 2.) He had no clear recollection of what happened immediately after the casualty but only a hazy memory of lying on a stretcher at a field ambulance where he had some tea. From there he was moved to a C. C. S. about twelve miles behind the line. Recollection of that hospital mostly concerned a pain which he felt in the left ear and which he attributed to an old otitis from which he had suffered since early youth, and which he thought had been lighted up by the journey on the stretcher with his head exposed. After three days he reached a base hospital in France from which he was transferred as a lying case to the First Northern General Hospital where he came under my care. When I first saw the patient, his only complaint was of some slight soreness about the situation of the wound on his chest. He lay still and quiet, but only because he had been told that he must take great care and insist on being carried. In general appearance he was a well-developed man with rather a big chest. He looked fit and well and made no complaint. At the onset I would like to say that this patient was of a calm and equitable temperament and with a sane outlook on life which throughout all the years I have known him has commanded my continued admiration and respect. Local examination disclosed a small wound of entrance one-half inch below and one-fourth inch external to the left nipple (Fig. 3), but there was no wound of exit. There were the scars of the through-and-through wound about two inches above the left elbow, but this had apparently done no damage and there was never any disability arising from it. The situation of the wound on the chest wall at once suggested the possibility of some cardiac injury, but there were no characteristic signs. The pulse was regular, steady, and of an average rate of 64 to the minute; the temperature was normal. There was no dyspnea, though, of course, the patient was kept quietly in bed. My colleague, Lieut.-Colonel Thomas Beattie examined the patient and reported as follows:

Received for publication, September 4, 1910.

"Slight deficient expansion on left side of chest. No impairment of percussion resonance. Breath sounds enfeebled vesicular over left base and axillary region but definitely audible and accompanied by some coarse crepitations. Vocal fremitus and vocal resonance present but diminished as compared with right side. Apex beat in fifth left interspace in nipple line. Heart action regular, no valvular defect, no pericardial friction."

An x-ray examination disclosed a service bullet with its base anchored probably near the tip of the left ventricle (Fig. 4). Not only was the foreign body pulsing with the regular heart beat, but its point was whirled about in the blood vortex in the heart cavity. Never before or since has it been my lot to witness a fluoroscopic examination which excited more vivid interest—a metallic foreign body which had



Fig. 1.



Fig. 2.

Fig. 1.—Contents of pocket traversed by bullet.

Fig. 2.—Notebook and scale perforated by bullet.

reached the heart cavity without killing the patient, and was merely anchored by its base to the heart wall, while its apex was whirling about in the blood stream like a weed growing from a stone at the bottom of a mill race. An electrocardiogram (Fig. 5A) was submitted to the late Sir James Mackenzie who kindly reported upon it as follows:

"The electrocardiogram shows nothing peculiar, excepting in the second lead where the wave T is inverted. This inversion of T was assumed at one time to be of serious significance, but I have watched cases who show it for a great many years, and this view has turned out to be unjustified. We do not know why T should be inverted. It is very well marked in your tracing. I shall be pleased if you will let me know how things transpire later."

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The operation was carried out on a never-to-be-forgotten Sunday morning, May 20, 1917, just thirty-nine days after the receipt of the casualty. Mr. W. E. M. Wardill and Mr. Rochester Smith acted as assistants, while Lieut.-Colonel Beattie and Major F. Pybus were also present. Captain H. H. Markham gave the anesthetic; induction was by A. C. E. followed by open ether, and this proved most satisfactory throughout. The approach was a left parasternal one and the general technique was as described by Kocher in the third English edition of his textbook, *Operative Surgery*.

Under the anesthetic it was noticed that the left chest did not expand as well as the right and that the intercostal spaces were drawn in a little. The skin incisions were as shown in the illustration (Fig. 3). As a first step the sixth costal cartilage was excised. There was no difficulty in carrying this out, and the pericardium was easily exposed by dividing the attachment of the triangularis sterni



Fig. 4.—The bullet in the heart.

along the seventh costal cartilage and the end of the sternum and pushing it outward and upward together with a good deal of fat. As soon as this had been done, air began to be sucked into the cellular tissue around the pericardium, to such an extent that this area rapidly became emphysematous. It closely simulated air in the pleura and throughout the operation was rather an anxiety, though it was controlled to some extent by covering up the exposed part with large wet swabs of gauze. The fifth and fourth rib cartilages were next cleared, the pleura being separated from their deep surfaces and gently pushed outward by the finger before they were divided.

The flap of chest wall was then bent outward, but, as this did not give enough working space, the third cartilage was also cut through and displaced. During this latter step the internal mammary vein was torn and almost at once the area became obscured by frothy blood which might have been a great nuisance, but

While the excitement of our discovery continued, the patient was apparently quite well and was finding enforced rest very irksome. On May 12 he was allowed to get up and as there were no harmful effects we both became bolder and the patient was allowed to go to the toilet, to walk about the ward, and to walk with care up and down stairs. He was taking ordinary food and smoking cigarettes in moderation as was his wont.

Meanwhile the proper management of the case was giving me earnest consideration. The bullet, I concluded, was not completely embedded in the heart wall but merely tethered by its base, the apex being free in the cavity. A priori it seemed that the patient ran a great risk with a foreign body in so precarious a position and I was fearful lest at any time it would become dislodged and cause fatal



Fig. 3.—Scar of wound, showing entrance of bullet just below left nipple; also the incision employed for exposure of the heart.

embolism or that blood clotting about the foreign body would produce a thrombosis which might behave in the same way. On the other hand the risks of its removal one knew must be considerable, but some few surgeons like Beausseant (Bull. Acad. de méd., meeting of May 4, 1915) of the French Army and others had already been rewarded by success. After summing up the situation and discussing the matter with my colleague, Lieut.-Colonel Beattie, it was proposed to the patient that I should at least make an attempt at the removal of the unwelcome visitor and he willingly agreed. In my own mind I determined that discretion should be the better part of valor, but, nonetheless, I felt very confident in judicious intervention especially as I pictured the possibility of the base of the bullet being visible on the outer surface of the heart wall.

lying there and palpation in the vicinity did not disclose its whereabouts. What was at first taken to be the bullet was felt to the right of the left coronary artery and at a spot near the junction of the auricle and ventricle, but the more this area was palpated the less did the hardness detected seem like a foreign body.

It must be remarked that the varying status of the heart muscle in systole and diastole made observations by palpation very difficult, for at the best diastole allowed only a second of relaxation, which is a very short time for accurate observation, and during systole the muscle became stony hard. After further negative palpation the region of the scar and the area near the ventricular base were explored by puncture with a straight needle but without striking anything metallic. The heart muscle was surprisingly tough and the punctures only bled momentarily. The region of the left auricle was then explored, but nothing abnormal could be detected.

It was still felt that the bullet might be lodged about the suspected area near the base of the ventricle. To steady the heart for final exploration a stitch of fine catgut was passed into the wall of the ventricle just by the side of the entrance scar. It was found difficult to manipulate a needle holder and in view of the possibility of having to open the heart and suture it rapidly a little more working space was felt to be necessary. This was secured by cutting away the sternal remains of the divided costal cartilages with rongeur forceps. This was a considerable help, but much more room could have been obtained by cutting away the edge of the sternum. Gentle traction on the stitch steadied this portion of the heart wall without in the least affecting its general action. Further punctures were made with the needle, but nothing metallic could be struck. In spite of these negative findings I was very reluctant to give up the attempt to locate what I imagined ought to have been an easily identified foreign body. As a last step it was decided to inspect and palpate the back of the heart, but we found that the organ could not be lifted forward without kinking the vessels to some extent, though it could be somewhat rotated on its long axis so as to expose partially its posterior surface.

The area high up behind the ventricle was thus exposed and then the whole heart was taken into the hand so that it could be thoroughly palpated between the fingers behind and the thumb in front. As a result something hard and elongated could be felt in the very center of the viscus, presumably about the base of the interventricular septum, and this was more like our foreign body than anything else. But this examination of the whole "heart in the hand" gave us a fright, for as soon as mild pressure was applied about the base it stopped beating. It was only after a few seconds that a furtive contraction was followed by one or two others which preceded a return to the regular rhythm and it was with thankfulness that the heart was allowed to return to its normal position in the pericardium. Having failed to locate the missile by external palpation, I wondered if an exploration of the interior of the ventricle was justified.

As the bullet had not, up to the time of operation, produced any symptoms and as it could not be certainly localized, I decided that it would be unreasonable to subject the patient to the risk of opening the heart cavity and the attempt to find and remove the bullet was therefore reluctantly abandoned. The area which had been traversed by the stitch was then dealt with. The needle punctures bled just a little and might perhaps have been left alone, but it was felt safer to cover them over with a suture of fine catgut passed Lembert fashion through the visceral pericardium. This was easily done and effectively controlled the slight oozing.

A little fluid which had collected in the pericardium was gently mopped up. In spite of a good deal of tension the edges of the pericardial sac were brought together with interrupted sutures of fine catgut passed so that the visceral surfaces were in contact with each other. A small drainage tube was left in the lowest part of the sac and another laid along the outside near the suture line. When

fortunately the vessel was easily caught and tied. Up to this time the respiratory movements had been rather labored and noisy, but they became quieter before the pericardium was incised. The latter was not distended and was readily opened by an oblique incision about two inches long made in the direction of the sixth cartilage.

Some small amount of blood-stained fluid escaped, but there were no clots and no adhesions so that one could only conclude that there had scarcely been any bleeding into its cavity. The incision in the pericardium was next prolonged upward by the side of the sternum to the level of the upper border of the fourth cartilage and later to the third; there was no bleeding from its cut edge.

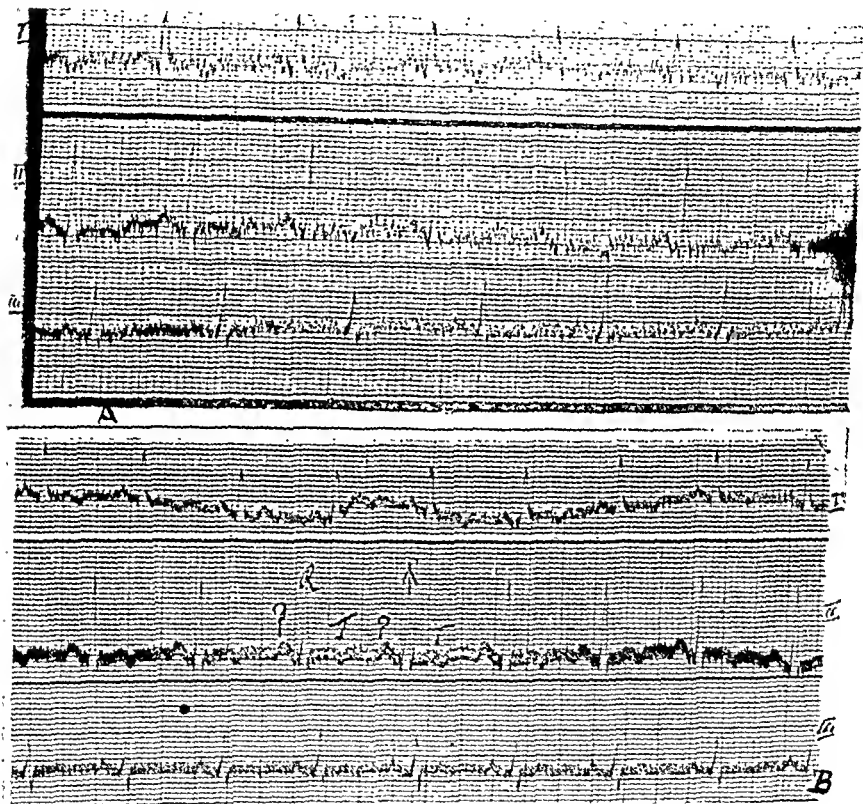


Fig. 5.—Electrocardiograms (limb lead) taken just before (A) and three months after (B) operation.

The heart, when first exposed, began to beat in a tremulous fashion, but this quickly ceased and throughout the subsequent manipulation its movements were very steady. Just after first administration of the anesthetic the pulse rate was 120 and of rather low tension, but at a later stage it was only 65 and of normal tension. At first sight of the naked heart nothing abnormal was noticed, but on further examination the spot where the bullet had entered was seen about the middle of the outer border of the left ventricle slightly toward its posterior aspect. It was a definite depression surrounded by a roughened whitish area on the visceral pericardium. Just opposite this point on the inner surface of the pericardial sac the scar of the wound of entrance was plainly seen. The heart muscle in the neighborhood of the wound felt firm, but I could not satisfy myself that the bullet was

capacity . . . I am not required to travel much . . . I conduct the work from an office in the County town, about seven miles from this cottage, which is well in the country, and I drive myself back and forward daily in a 10 h.p. car.

"The heart has not troubled me much and so far as I can gather from such doctors as I have had to 'listen in' from time to time it appears to be working normally. I have not felt it necessary to consult a specialist at any time. Remembering the teaching, I have just been going easy physically. I have not worried about games, I mean golf, etc., for a long time. I find that with my gardening when the weather is good, I can get all the exercise I want. . . .

"As a matter of interest to you, I had my appendix removed about five years ago. A surgeon in Edinburgh did it, using a local anaesthetic. I got over it all right. I think I was back to this office in a month or five weeks. . . ."

A year later, in June, 1937, that is, just over twenty years from the time of the casualty, I had the pleasure of a visit from the patient, when the following note was made:

"The Captain came to see me. He is now staying in London for a little holiday. He informs me that on the whole he is very well and has no disability of any sort so far as his heart is concerned. He still lives in the country and usually drives his own car to his office, but when the weather is fine, he walks one and a half miles to the nearest village and gets a 'bus, but he does not do that in cold weather. During recent years he has been occupied in making a garden and works a good deal himself. He gave up golf a few years ago, not because he found it did any harm but because he thought it would perhaps be wiser not to exert himself unduly.

"At times he has suffered from indigestion, or what he calls indigestion, which has taken the form of a pain in the epigastrium, but it has never been very bad.

"He is now fifty-two years of age, and looks very well though rather heavy and with an obese abdomen. The scar over the pericardium looks perfectly normal in every way; it is firm and gives no trouble. The Captain made no complaint except of his ear, which was troubling him a good deal. Dr. Duncan White made an x-ray examination and reported:

"A bullet is embedded in the wall of the left ventricular septum. Its movement is synchronous with the cardiac contractions. There is slight enlargement and rounding of the left ventricle with very slight unfolding of the aorta." (Fig. 4.)

Dr. R. S. Aitken, now Professor Aitken of Aberdeen, made an examination of the chest, and except for some emphysema there were no signs of disease. The heart appeared to be normal and the pulse ranged about 62 and was perfectly steady. The blood pressure in three readings averaged 138/88. At the same time Dr. Paul Wood made an electrocardiogram which he reported as being entirely within normal limits (Fig. 6). At the same time I took the opportunity of asking Dr. Wood to let me have his observations on the previous electrocardiograms, that is, those made just before and just after the exploration, as I knew that much light had been thrown on cardiographic problems since the time the patient first came under observation. The following is his comment:

"These electrocardiograms, showing inversion of the T wave in Leads 1 and 2, often with a diphasic effect, probably signify haemopericardium in the first instance and healing of it in the second. Alternatively they might indicate an injury to the anterior wall of the left ventricle. If the bullet entered the left ventricle anteriorly it is impossible to say whether the muscular injury or the associated pericardial lesion was the cause of the electrocardiographic findings, but it was certainly one or the other. If the bullet did not damage the anterior wall of the left ventricle, then the pericardial lesion can be blamed with certainty. Not much blood in the pericardial cavity would be necessary.

the wet gauzes which had been used to protect the cellular tissues were removed, the emphysema of the latter was very obvious and rather embarrassing. With each expansion of the chest the pleura was forcibly advanced and it was realized how easily it might have been injured, had it not been for the gauze protection. The flap of chest wall was readily laid back into position and was held by one or two catgut sutures between the periosteum of the sternum and the perichondrial structures, but since the sternal ends of the costal cartilages had been cut away perfect apposition could not be secured. The skin was sutured with interrupted silkworm without tension, the drains being brought through the center of the lower oblique incision. The area was supported by strapping firmly applied over the dressing with an encircling chest bandage over all. The operation took one and three quarters hours, the greater part of that time being expended in efforts to locate the bullet.

The patient stood the ordeal perfectly well, though at the conclusion he was rather cyanosed, but the pulse was slow and of good volume when he left the table. Immediate recovery was satisfactory and gave no cause for anxiety. On the second and third days, with a respiration rate of 30, the pulse was over 100 but it was never more than 110 and soon came down to between 80 and 90 and then 70 and 60, and the rhythm was regular throughout. The only troublesome symptom was persistent vomiting without nausea, and this was really distressing. For days he could keep nothing down, but in spite of this seemed well and was quiet and undisturbed. In the course of a week the condition gradually subsided, having been entirely uninfluenced by treatment. The patient himself dated his revival from about the fifth day, when he expressed a great longing for a whisky and soda. Like everything else that he took this was promptly rejected, much to the discomfiture of the nurse, though the patient declared that he enjoyed it "both going down and coming up again," and he certainly began to improve from that time and eventually recovery was satisfactory. He was well enough to be out of bed in three weeks. The wound healed per priam, though the patient felt some weakness over the area and a sense of "coming apart" on coughing or exertion, but this gradually lessened and five weeks after operation, when he began to walk, the area was firmly consolidated and the chest expanding well. A month after operation Col. Beattie made an ordinary examination of the heart without finding signs of abnormality. A further x-ray made at this time showed the bullet in precisely the same position as before and moving with the heart beat, but the whirling movement which had been so striking a feature had ceased.

The patient left the hospital nine weeks after operation and thereafter steadily improved. Three weeks later the condition was good with the heart behaving well. An electrocardiogram made at this time showed the same appearances as before the operation (Fig. 5B). In November he reported himself as very well and shortly afterward he took up adjutant duties and next year was transferred to the records office of his regiment. After taking his discharge early in 1922, he took a long rest before resuming civilian occupation in an office. Thereafter he was able to do all ordinary things in moderation including playing a mild game of golf. Ten years after operation he married. At times he was perhaps rather apprehensive and a little too careful. In consequence he put on weight unduly and suffered from indigestion. In 1934 I had a report as follows:

"... the heart seems to be in pretty good condition. It is not enlarged, sounds are good and the rate normal. His blood pressure about 135 . . . he has not been taking enough exercise to keep himself fit."

After that date the best epitome of his activities is that contained in a letter which I received in July, 1936, just nineteen years after the casualty.

"You will observe from the above that I have moved further North. Well, as to the past years since you heard of me—about ten years ago I obtained employment as Taxation Officer, which has proved fairly suitable for my physical

walls of those cavities are so much thinner and so easily torn that death from hemorrhage is to be expected. Nonetheless, in Decker's series no less than 8 of the examples of the 65 retained missiles were in the auricles. As the result of his review and of his great experience in military surgery, Makins suggested that when death was immediate it was as likely to be due to shock as to hemorrhage. He also stated that probably a spent bullet would be much more likely to lodge in the heart. This point is strikingly illustrated by the case reported by Birkbeck, Lorimer, and Gray<sup>3</sup> in which a bullet was lodged in the right ventricle. In that case the bullet had "passed through and killed a man in front of him."

In the case now reported there is no certain information as to the distance which the bullet traveled before striking its victim, but the fact that it probably traversed the upper arm and certainly the large wad of paper material in the breast pocket was probably enough to slow up its velocity and possibly determine its lodgment. (The ventricular wall may be perforated by a missile not only without serious hemorrhage into the pericardium but with practically no bleeding.) The impaction of the bullet in the heart wall may act as a plug and in some cases<sup>4</sup> the bullet has actually been found so situated, the base projecting slightly from the outer cardiac wall. Deposit of clot around the bullet may also play a part, but probably the powerful contraction of the heart muscle is the most important factor. Anyone who has witnessed the extreme contractile power of the heart muscle in vivo will have no difficulty in realizing that this in itself would probably be enough to close the tract of the bullet and to prevent any but trivial hemorrhage; this is certainly borne out by the experience of this case. At the operation there was only a small amount of blood-stained fluid in the pericardium and no evidence that there had ever been free hemorrhage. In stab wounds of the heart (Fig. 7) the condition seems to be rather different for there is usually free bleeding, but even so the actual loss of blood is often not enough in itself to kill the patient, death usually occurring because the collection of blood in the pericardium compresses the heart and leads to the condition known as "cardiac tamponade," which is usually the cause of the immediate fatality. When a bullet is lodged in the heart wall without causing immediate mortality, what is the reaction of the surrounding tissues to the intruder? It may be safely asserted that in the absence of infection encapsulation by fibrous tissue will occur.

That this process was taking place was suggested in the case under consideration by the fact that the whirling movements at first seen on fluoroscopic examination gradually ceased as though that part of the bullet projecting into the heart cavity were becoming gradually covered by organizing clot which would be provided by a smooth endothelial covering. Exactly the same thing appears to have occurred in the case

"The graphs are, of course, quite abnormal, and I can say with certainty that there could be no other cause for them in this case. They are rather more like the changes due to haemopericardium or to other pericardial conditions than those of anterior left ventricular injury. . . ."

In April of this year (1940)\* the patient reported that he was quite well, though he confessed to being a little tired, "a result of the present war, not the last one!" When fatigued he suffers from what he describes as indigestion, but this passes off after a week or ten days' rest.

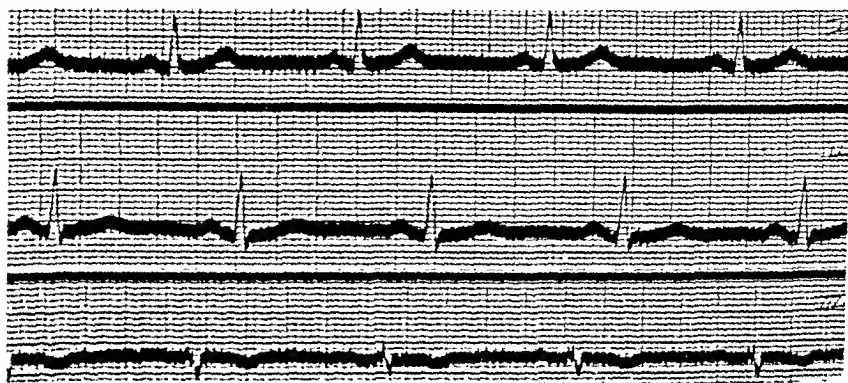


Fig. 6.—Normal electrocardiogram with bullet in situ in left ventricle twenty years after casualty.

Considering the magnitude of the last great war with its multiplicity of arms and its huge toll of casualties, it is surprising that there are comparatively few records of patients long surviving with bullets lodged in the heart. That there are still fewer cases where a fragment of shell has been retained is almost certain, because wounds caused by these fragments are so frequently fatal as a result of infection. Further, many foreign bodies supposed to be in the heart are really imprisoned in some part of the pericardium. In a recent review of the subject Decker<sup>1</sup> was able to quote from 100 case reports of foreign bodies retained either in the heart or pericardium and of these 65 were bullets or fragments of shell in the heart itself. Probably there are many more examples than have been recorded and some indeed may be unknown, for, strange though it may seem, there are those who were wounded in the late war who have never been submitted to x-ray examination. All those who have looked into this matter have been struck by the number of cases in which portions of missiles imprisoned in the heart have apparently not given rise to inconvenience much less serious symptoms, a wonderful tribute to nature's powers of repair. In his interesting review of "Specimens Showing the Effects of Gunshot Injury on the Heart and Blood Vessels in the War Collection at the Museum of the Royal College of Surgeons of England" Makins<sup>2</sup> suggests that bullet wounds of the ventricles need not necessarily end in fatality. It should be observed that wounds of the auricle are different, for the

\*April, 1941, patient very well just twenty-four years after the casualty.

Zealand in 1860. "There were doubts as to whether or not the bullet had penetrated the chest so trifling were the symptoms." The man lived for fourteen years and then died in Ashantee from remittent fever when the bullet as shown in the specimen was disclosed at the post mortem.

It is surprising that many missiles have remained quite free in the cavities of the heart, from which they have been removed at considerable intervals after the casualty and often with success. When loose in the cavities, they may leave the heart with the blood stream and become lodged in one of the great vessels. Indeed there seems to be no end to the vagaries of these unattached and unwelcome visitors. On the

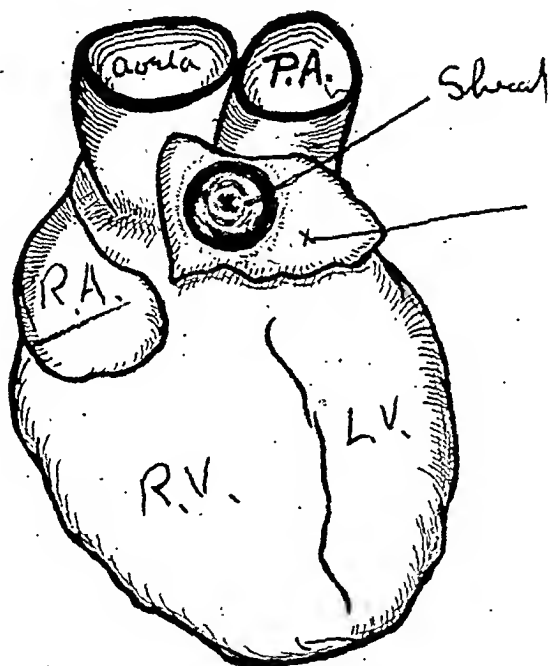


Fig. 8.—Leaden ball encysted outside pericardium and discovered at post mortem fourteen years after wound. At the time of the casualty the symptoms were trifling. Death was the result of a tropical fever. (From Army Medical Museum, Millbank.)

other hand, a wound in the heart, however produced, may result in a weak scar which may subsequently rupture either spontaneously or as the result of violence or may gradually yield, to be followed by the development of an aneurysm of the viscus. Late dislodgments of a foreign body may also occur. The symptoms associated with impacted foreign bodies which have produced neither immediate nor rapid death and have settled down in the organ also vary. The case under consideration shows that there may be an entire absence of symptoms and, indeed, except for the disclosure of the x-ray, the presence of such a thing as a foreign body in the heart might well be doubted. It is recorded (Decker) that some patients who harbor foreign bodies in the

recorded by Burgess.<sup>4</sup> I have not been able to find an illustrative specimen either in the Museum of the Royal College of Surgeons of England, the Army Medical Museum at Millbank, or the Museum of the Medical School at Newcastle-on-Tyne. But the state of the parts has been mentioned by some surgeons, and Couteaud and Bellot,<sup>5</sup> recording a case where a bullet was lodged in the wall of the auricle from May 14 to Nov. 9, state that "the vigorous fibrosis which surrounded the

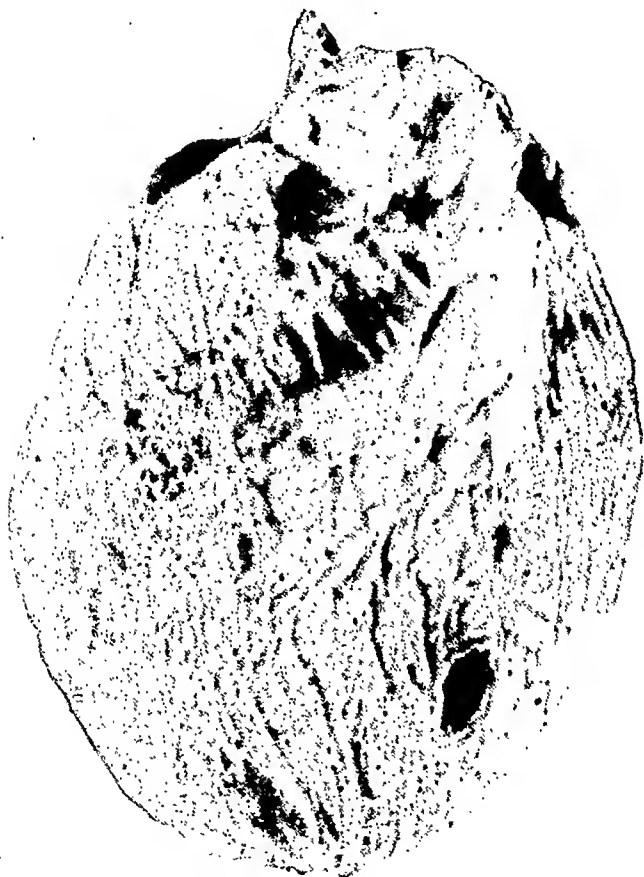


Fig. 7.—Stab wound of left ventricle produced by an Arab dagger.

bullet resembled a veritable fibroma, its capsule averaging  $1\frac{1}{2}$  centimetres in thickness." In another published case the bullet is said to have become encysted. In the Museum of the Army Medical College at Millbank there is a specimen of a heart with a piece of the anterior pericardium and lying on the outer surface of the latter, just opposite the root of the great vessels, is an old-fashioned lead musket ball (Fig. 8). The catalogue description states that the man was wounded in New

circumstances the problem is entirely different. If a foreign body in the pericardium is causing symptoms, it ought to be possible to remove it comparatively easily and with little risk, and no competent surgeon need hesitate to undertake the intervention. In two cases (Figs. 9 and 10) in which I operated the foreign body was the cause of an external sinus. Both were imbedded in the pericardium, and it was not difficult to remove them, using an incision by the side of the sinus and excising cartilage. For merely opening the pericardium for purposes of exploration or for removing a loose body in that cavity, an incision in Larré's angle ought to be very satisfactory. When the foreign body is fixed and anterior, it may be reached by the nearest route from the surface, which will usually mean making a parietal incision along one of the lower costal cartilages on the left side. Should the missile be

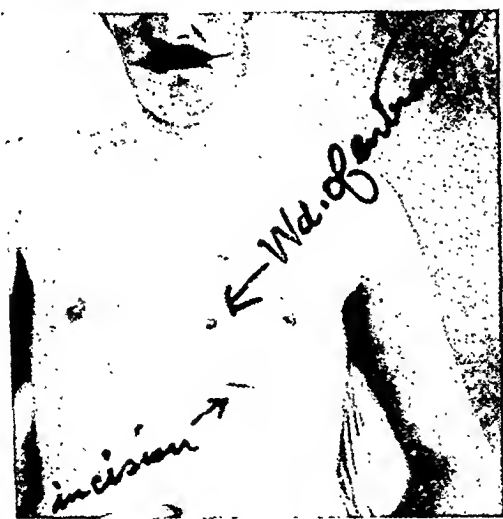


Fig. 9.—Bullet wound over pericardium. Patient wounded in November, 1916. Free discharge of pus from the track which healed and broke down many times. Removal of foreign body in August, 1917, followed by good recovery with complete healing.

on the posterior surface or the lateral walls, the Kocher approach is probably the best. I have no experience in the extraction of the foreign body under the fluorescent screen, a small incision having been made into the pericardium from the surface of the chest. This is a method suggested and practiced with success by some French surgeons. In fortunate circumstances this may be successful, especially with a foreign body loose in the pericardium and sometimes perhaps if the foreign body is merely attached to the outer surface of the heart, but I cannot imagine it being successful in other circumstances. Just prior to any operation for the removal of a foreign body, the exact position of the object must be again confirmed by careful x-ray examination. It is quite remarkable how the movements of the heart may be communicated to a foreign body which is not really in that organ. On occasion

heart have done heavy work, such as coal heaving, and that one man climbed a mountain 2,000 meters high. On the other hand there may be attacks of palpitation, irregularity of heart action, and dyspnea or syncopeal attacks on exertion. In some cases pain has been a marked feature, either precordial or retrosternal and either sharp or dull. Sometimes the trouble is more a sense of oppression over the heart. In some cases the symptoms follow close on the injury, but as a rule such early troubles settle down as the result of the long period of rest which is enjoined and in about one or two years cases that are going to do well should be symptom free. In others the symptoms only occur when an attempt is made to resume active normal life. The differences in the consequences probably depend on the position of the foreign body in the heart and especially its relation to the muscle bundles and the co-ordinating centers. In addition to the characteristic cardiac symptoms just mentioned there may be neurotic manifestations which mainly depend on the attitude of the patient to the knowledge that he harbors a foreign body in one of the citadels of his well-being. Patients who have felt no evil consequences have sometimes been kept in thralldom by the well meaning attentions of overanxious relatives or friends.

The management of these cases is a matter for serious consideration. A patient who has fortuitously survived a casualty so menacing deserves to be very closely guarded against ill-advised attempts at surgical intervention. In the case which is here recorded the attempt to remove the missile appeared to be justified for the reasons already stated, but at that time there was little to guide us as to the natural history of bullets in the heart. The experience that has since accumulated has shown that in the process of time many foreign bodies, perhaps most, become safely encysted and do no harm. The fear of infrequent late complications (Decker quotes Loisson that there were 9 cases of late rupture of cardiac aneurysm in 254 cases of heart injury) should not be made an excuse for intervention when the patient is symptom free, and it would seem a good rule to leave the foreign body alone unless the heart continues to rebel against its presence. The interpretation of the disclosures of the electrocardiograph may furnish some guide as to when intervention is in the best interests of the patient. On the other hand, if definite symptoms persist or develop, then intervention of course, should be seriously considered, and the operation for removal of missiles from the heart has now many brilliant successes to its credit. The situation of the foreign body has a decided bearing on the question, for those situated in the ventricles or near the apex have proved much easier problems than when the auricles are involved or when the lodgment is in the posterior surface of the organ. I am not here and now concerned with the question of foreign bodies in or about the pericardium, but it may be observed that in those cir-

The parasternal approach of Kocher gives an admirable exposure of both ventricles and the lower part of the auricles and by lifting up and rotating the organ its posterior surface can be reached. The trans-sternal approach gives a freer exposure of the auricles, especially the right. The original plan of Kocher was employed in the case here recorded and proved very satisfactory. From my experience with this case and the study of dissections made for me by my colleague, Mr. A. K. Henry, I feel satisfied that it is efficient. Study of the exposure of the dead rigid immobile heart as found in the cadaver is illusionary. The living organ is more accommodating for it stands forward in a striking way, but the difference in size when the organ is in systole is very remarkable, nonetheless, its constant movement is embarrassing. As Kocher always insisted, every surgeon ought to be prepared to expose the heart in emergency and for most general purposes the method associated with his name will prove satisfactory. In these times it may not be inappropriate to set out the steps of this useful operation. These are as follows:

1. Incision from center of sternum along sixth costal cartilage as far as the mammary line. This divides all the soft structures down to the cartilages, including the costal attachment of the rectus abdominis.
2. Separation of the perichondrium and excision of the cartilage, the separation to be commenced at the sternal end, the junction with the seventh cartilage being divided. This exposes the mammary artery and vein a finger's breadth from the edge of the sternum. These vessels should be ligatured and divided.
3. Make a vertical incision through the triangularis sterni muscle close to the sternum.
4. Gently thrust this muscle outward. This will carry the pleura out of harm's way and expose the pericardium which can be opened either now or at a later stage.
6. To secure more room, make a vertical incision up middle of sternum to level of third or even second rib; in a bulky subject make an incision along one or other of these cartilages for three or four inches.
7. Separate the periosteum of the sternum outward until costal cartilages are exposed.
8. Separate the intercostal muscles from the borders of the cartilages and gently insinuate finger behind each just by edge of sternum. Divide fifth, fourth and third cartilages at their inner ends.
9. Lift up flap with a view to turning it back to the left. Do this slowly and gently push pleura outward as the cartilages are elevated.
10. Break cartilages at junction with ribs, thus exposing a considerable area of pericardium.
11. Carefully palpate state of affairs through pericardium.
12. Open pericardium along edge of sternum and, if necessary, outward at lower end of exposure.

it may require great knowledge and skill on the part of the radiologist to state with assurance the exact situation of foreign bodies about the heart. The technique of operative intervention turns largely on the question of exposure. Although general anesthesia has usually been employed, many operations have been successfully carried out under local anesthesia alone. A whole variety of methods can be employed and they fall into two groups (1) those where the approach



Fig. 10.—Gunshot wound over pericardium. Patient wounded in June, 1916; thereafter wound healed and broke down many times. Seen June, 1918, with foul discharge from the sinus, the mouth of which was tucked in with every heart beat. Excision of two cartilages with removal of foreign body (shown in insert) resulted in complete recovery.

is parasternal represented by (a) the original Kocher flap method, (b) cartilage and rib resection, (c) the intercostal approach where the ribs are spread and the pleural cavity opened, (2) the trans-sternal approach in which the body of the sternum is vertically divided and the halves forced apart; as a modification it has been suggested that the body of the sternum may be removed. The method to be employed is largely decided by the part of the heart which it is desired to explore.

13. To secure further space use rongeur forceps to cut away remains of sternal ends of costal cartilages and, if required, part of the sternum.

These steps are shown in Figs. 11, 12 and 13, slightly modified from Kocher's well-known textbook on *Operative Surgery*. The great thing is to work from below to keep near to the sternal edge and to push the structures gently outward. It assists separation of the pleura if some local anesthetic is injected into the extraperitoneal tissues.

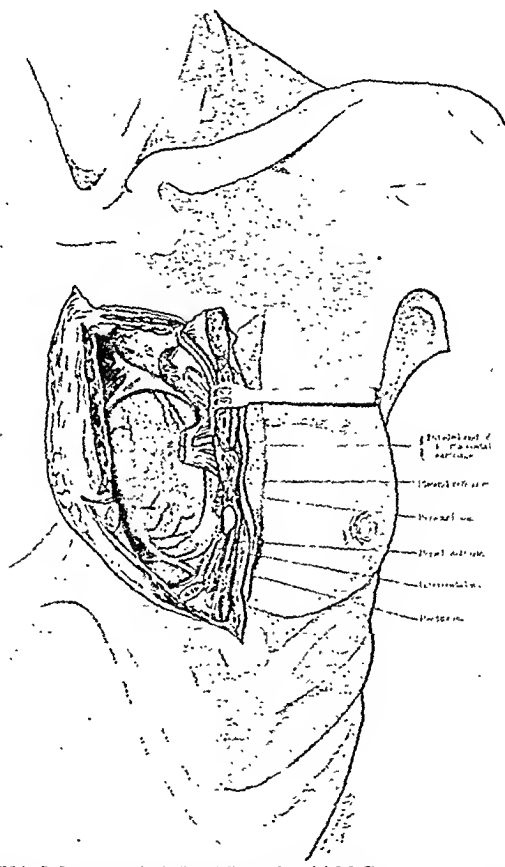


Fig. 13.—Exposure of the heart. The sixth rib is resected; the fifth, fourth, and third costal cartilages are divided and retracted outward along with the pleural reflexion (after division of the triangulæris sterni). The internal mammary vessels are seen ligatured and divided, and the pericardium is fully exposed. (Modified after Kocher.)

The intercostal approach with free opening of the pleural cavity exposes the patient to all the risk of pneumothorax without compensating advantages. Though the method is rapid, it must be remembered that some form of positive pressure anesthesia should be employed. In the presence of a pneumothorax with a wound of the lung the method is ideal. The fourth costal cartilage and corresponding portion of the rib are excised and the pleura opened to the extent of the

## SURGERY

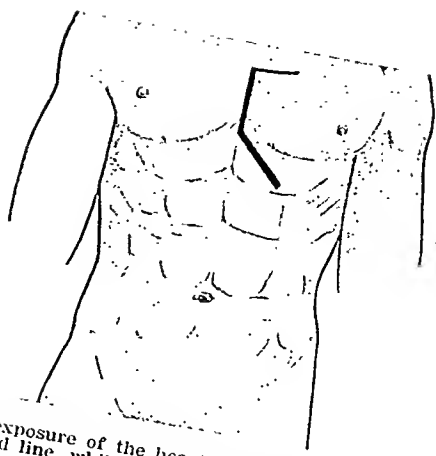


Fig. 11.—Incision for exposure of the heart. The primary incision along the sixth rib is indicated by a broad line, while the transverse cut along the third (or second) rib is represented by a finer line. (Modified after Kocher.)

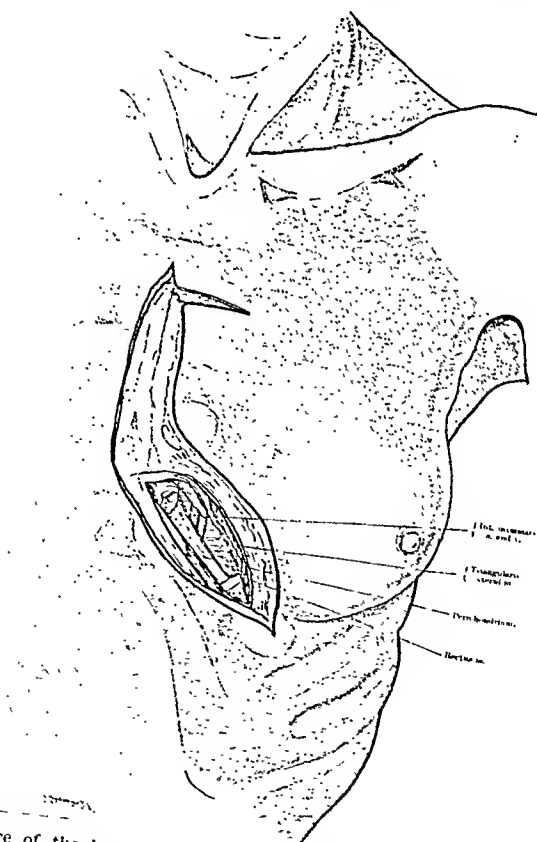


Fig. 12.—Exposure of the heart. The skin and fascia are divided, and the sixth costal cartilage resected. The perichondrium is exposed lying on the triangularis sterni, on which also the internal mammary vessels descend. (Modified after Kocher.)

possible exposure by incision of the pericardium to the limit of the parietal incision. After exposure by any of these methods the heart may be inspected and palpated with ease so far as its anterior surface and borders are concerned. To steady the heart for more deliberate palpation or for suture or incision it is usual to put a suture into its substance near the apex; that is, where the muscle is thick and the cavity not so near the surface. This suture should be of fine silk or No. 1 chromicized catgut and must take a hold about one-third inch deep. By making gentle traction upon it, the heart may be steadied, but, if it is pulled upon, the stitch may cut out. When it comes to locating the foreign body, the utmost gentleness must be used. It is fortunate when the foreign body projects somewhat from the cardiac wall. The difficulties in locating a foreign body are sufficiently indicated by the recital of this case, but other operators have been more fortunate and doubtless more skillful. Palpation in certain areas or pushing the heart to one side or lifting it forward may cause great irregularity in the beats or even cessation. But these phenomena only continue while the abnormal stimulus is applied and when that ceases the organ usually quickly resumes its normal rhythm or does so in response to gentle stroking or very gentle squeezing applied away from the inhibiting area. All handling should be done very carefully and gently, and, if the heart shows signs of resentment, all manipulation must stop for a few moments. When the heart is to be incised, there is always the question of hemorrhage and every surgeon seems to have prepared for this eventuality by putting in sutures first and cutting between them. If profuse bleeding occurs, it may be controlled by placing the finger over the point, but great care must be taken not to thrust the finger into a softened heart. Entry of blood by the vena cava may be controlled by placing the ring and little fingers behind the base of the heart and compressing these great vessels between those fingers and the middle finger in front, thus leaving the index finger and the thumb free to carry out manipulations on the anterior surface of the organ. This maneuver is known as the Sauerbruch grip. It is said that this grip may be kept up for as long as ten minutes with safety. It is important to limit any incision into the heart muscle to the smallest proportions so that it ought to be made directly over the foreign body. It is, of course, essential to avoid injury to the coronary arteries and their branches not only when making an incision, but also in placing any sutures that may be required to close it. When the foreign body is reached, it should be grasped with strong forceps so that by a process of rotation and manipulation it may be coaxed out of a very small wound. The edges of the incision must then be closed by suture. If there is profuse bleeding, this may be somewhat controlled by crossing the guide sutures firmly over the incision while the stitches are introduced. The latter may be of fine silk or No. 000 chromicized catgut.

incision. The space is enlarged by using the rib spreader. The pericardium is readily seen and can be opened to any required extent. At the termination of the intervention the pericardium may be closed by suture, though it is sometimes recommended that the sac should not be completely closed so that drainage can occur via the pleural cavity.

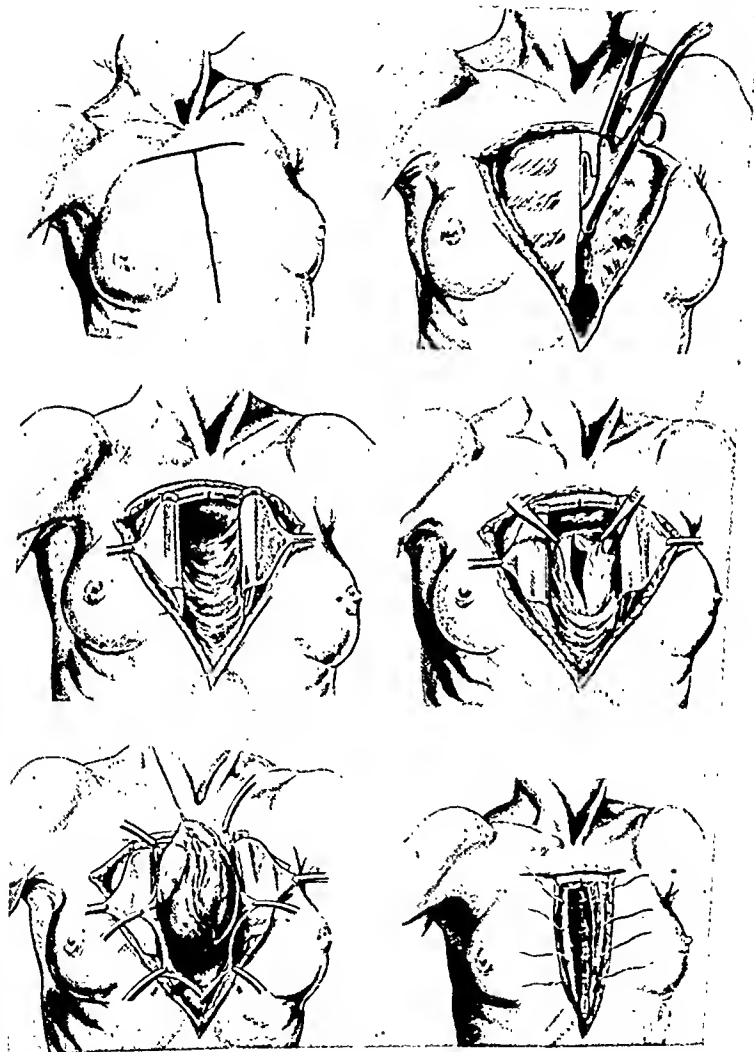


Fig. 14.—Trans-sternal approach to pericardium and heart. (After Sauerbruch and O'Shaughnessy.)

I have no personal experience with the method of splitting the sternum other than as a cadaver operation. It involves considerably more traumatism than the Koehler plan and does not appear to give as good a general exposure, though the right side of the heart is more accessible. The two halves of the bone are thrust aside by using a rib spreader (Fig. 14). When necessary, full use must be made of the

## THE EXCRETION OF SULFANILAMIDE AND SULFAPYRIDINE IN HUMAN BILE\*†

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AN IMPORTANT therapeutic factor possessed by sulfanilamide and sulfapyridine is the facility with which these drugs diffuse to all tissues and fluids of the body, including the liver and bile. While there is available information concerning the excretion of sulfanilamide in human bile, studies have not been recorded in the literature relative to the biliary excretion of sulfapyridine. Bettman and Spier<sup>1</sup> administered sulfanilamide preoperatively to each of eleven patients shortly before a cholecystectomy was done. Quantitative determinations of sulfanilamide were carried out on specimens of gall bladder bile and venous blood and they concluded from their data that the drug was excreted in the bile and concentrated in the gall bladder. Hubbard and Anderson<sup>2</sup> made the important observation in human subjects that, following the ingestion of sulfanilamide, larger amounts of acetylated sulfanilamide appeared in the blood as compared to the concentration in bile draining from a T-tube. Investigations of a similar nature have been made with laboratory animals. Studying the excretion of bile sulfanilamide in chronic bile fistula dogs, Carryer and Ivy<sup>3</sup> found that, after a single oral dose, sulfanilamide appeared in the bile within two hours and the usual maximum concentration was reached within four to six hours. They stated that the total excretion of sulfanilamide in the bile was relatively low. Observations of the same order were made by Manche, Plotner, and Siede,<sup>4</sup> who gave neoprontosil to dogs with bile fistulas. On the basis of their experimental studies, they administered the drug to patients with infections of the biliary tract and reported favorable clinical results.

It is apparent that more precise information is desired relative to the excretion of the sulfonamide compounds in human bile. The purpose of the present study has been to determine simultaneously the concentrations of sulfanilamide or sulfapyridine in the blood and bile under various conditions. In the manner to be described, it could be ascertained how quickly the free and conjugated forms of the compounds appeared in the bile compared to blood, when the maximum concentrations

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†Sulfapyridine was supplied by the Calco Chemical Co. and acetylsulfanilamide by the Winthrop Chemical Co.

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Should the heart muscle prove very friable a strand of suture passed parallel to the incision will act as a support for the approximating sutures, just as when used for dealing with the solid viscera. No one who has not had the experience can appreciate the embarrassment caused by the ceaseless movements of the heart. Even if bleeding does not cease at once, it will probably do so in a short time, especially if assisted by the pressure of the finger. The pericardium is closed by suture, but unless the sac has been distended the edges do not approximate very readily. Apposition is best secured by commencing at the upper extremity and carrying the suture downward. It is probably a help to interrupt the suture at a couple of points.

When there is any question of infection or of continuous oozing, it is probably safer to provide for drainage either by leaving a small tube, the edge of which is just within the pericardium, or by leaving the lower end of the incision unsutured for one-half inch. Some surgeons have had cause to regret that provision for drainage was omitted.

In the paper by Decker already referred to, he states that the late mortality of foreign bodies in the heart is about 20 per cent and that the mortality of operations for their removal has been the same. There have certainly been many brilliant achievements in this field of surgery, but probably many unsuccessful results have escaped publication and it is likely that the risks of the operation are rather understated.

The management of cases of foreign body in the heart in which the patients have survived the immediate dangers of their implantation must be settled on general surgical principles. Academic considerations and a knowledge of the fate of foreign bodies in the tissues generally would suggest a more frequent resort to operation than is wise. Nature at least should be assisted to exhibit her powers as a healer and the patients suffering from cardiac disability after gunshot wounds should have many months of rest. If, in spite of a fair chance, cardiac disability persists or develops after a period and interferes with usefulness, the aid of surgery may properly be invoked. The difficulties may be very great and even during operation a wise restraint may save a disaster. As the late Frank Jeans of Liverpool was fond of saying: "A living problem is better than a dead certainty."

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dose of the drug, smaller doses were given every four hours. Likewise, a single large dose of acetylsulfanilamide was administered to each of three human subjects and similar observations made. When it had been established that the acetylated form of sulfanilamide could be safely given to human beings, observations were then made in individuals with T-tubes.

## RESULTS

Data concerning the concentrations of sulfanilamide in bile and blood are recorded in Table I. Data pertaining to sulfapyridine are presented in Table II. The outstanding finding in both groups of observations was the appreciable concentration of both sulfanilamide and sulfapyridine that was attained in bile when therapeutic doses of the drug were used. The initial levels of both sulfanilamide and sulfapyridine were lower in the bile than in the blood. It is of interest that the maximum level of bile sulfanilamide was lower than the blood sulfanilamide in all four patients. On the other hand, a much greater concentration of sulfapyridine was obtained in the bile, when compared to the blood, in two of three patients. In general, less of the conjugated forms ap-

TABLE I  
CONCENTRATION OF SULFANILAMIDE IN BILE AND BLOOD

PATIENT	DOSE	HOURS AFTER INITIAL DOSE	MG. PER 100 C.C. IN BILE			MG. PER 100 C.C. IN BLOOD		
			FREE	TOTAL	PERCENTAGE ACETYLATED	FREE	TOTAL	PERCENTAGE ACETYLATED
J. B., 55- year-old female	‡ Gm., then 1 every 4 hr.	4	1.0	1.04	3.85	4.94	6.0	18.4
		6	6.3	6.6	4.55	8.2	14.1	41.8
		24	15.2	16.4	7.3	16.1	28.0	42.9
		48*	11.5	13.0	11.5	18.2	21.7	16.1
		72	9.2	9.3	10.2	9.5	12.1	27.4
		96	3.2	3.4	5.9	4.0	5.0	20.0
	Total, 16	120	1.0	1.1	9.2	Trace	1.0	---
F. W., 49- year-old female	‡ Gm., then 1 every 4 hr.	4	5.0	5.2	3.85	18.2	23.0	20.8
		6	13.3	13.7	2.9	15.2	23.3	34.7
		24	13.4	13.6	1.5	14.5	20.0	27.6
		48*	8.6	9.8	12.2	10.5	16.0	34.4
		72	7.8	8.8	11.3	3.87	8.0	51.2
		96	Trace	Trace	---	Trace	1.66	---
	Total, 16	120	Trace	Trace	---	Trace	1.9	---
O. H., 68- year-old male	‡ Gm., then 1 every 4 hr.	16	6.7	8.2	18.3	11.9	14.7	19.0
		40	7.4	8.6	14.0	11.8	20.0	41.0
		64	8.7	8.9	2.25	15.5	20.0	22.5
		88*	8.8	10.4	15.4	16.5	23.4	29.5
		112	3.35	3.9	14.0	3.85	8.35	54.0
		136	1.23	1.47	16.3	Trace	4.05	---
		160	1.39	1.46	4.8	Trace	5.10	---
		184	1.10	1.27	13.4	Trace	5.3	---
		208	Trace	Trace	---	Trace	2.14	---
	Total, 20							
R. N., 47- year-old male	‡ Gm., then 1 every 4 hr.	16	---	---	---	9.5	13.8	31.1
		24	2.2	2.4	8.3	9.2	10.1	8.2
	Total, 14							

\*Sulfanilamide discontinued.

were reached in these media, and over how long a period of time the drugs could be detected in the bile and blood after oral administration was discontinued. Another phase of the present study depended upon the knowledge that sulfanilamide is acetylated in the liver.<sup>5, 6</sup> This is likewise probably true for sulfapyridine. Because of this, it appeared important to confirm and extend the observations of Hubbard and Anderson<sup>2</sup> and to determine whether more of the acetylated forms of both sulfanilamide and sulfapyridine appeared in the bile than in the blood.

#### METHODS AND MATERIALS

Essentially two methods of study were used. The first group of observations were made upon five patients who had had a cholecystectomy and choledochostomy and a T-tube inserted into the common bile duct. This permitted a collection of hepatic bile at the bedside. Several months after their operations, with the T-tubes still in place, these patients were given sulfanilamide or sulfapyridine orally and the levels of the absorbed drugs were determined simultaneously in specimens of bile and blood collected at intervals. An initial dose of 4 Gm. was administered and then 1 Gm. every four hours thereafter. It should be pointed out that the total amount of the drug excreted in the bile could not be determined, since only a part of the bile flow was diverted through the T-tube. Fortunately, there was a continuous flow of bile through the choledochostomy tubes of all the patients. The method of Marshall and Litchfield<sup>7</sup> was used for ascertaining the levels of the free and conjugated forms in the blood, while we employed the procedure of Doubilet, as described by Carryer and Ivy,<sup>3</sup> for determining the levels in the bile. The bile obtained from two patients was cultured before any drug had been administered and then again at intervals, after sulfanilamide and later after sulfapyridine had been given.

A second method of studying this problem depended upon the oral administration of acetylated sulfanilamide to seven additional patients with T-tubes in the common bile duct. Four grams of acetylsulfanilamide were given and then 1 Gm. every four hours for five doses. Simultaneous determinations of the concentration of free sulfanilamide and acetylsulfanilamide were made at intervals upon bile and blood. In this manner we desired to obtain information concerning the excretion of preformed acetylsulfanilamide by the liver. Before giving the drug to human subjects, it was administered to dogs and observations were made relative to the absorption, blood concentration, excretion, and toxic manifestations. An aqueous suspension of acetylsulfanilamide was introduced through a tube into the stomachs of two animals under fasting conditions. The concentration of both free and conjugated sulfanilamide was then determined in the blood at various intervals after the single dose had been given. In a third dog, after it received the initial large

TABLE III

BLOOD CONCENTRATIONS OF FREE AND ACETYLATED SULFANILAMIDE IN ANIMALS RECEIVING SINGLE DOSE OF ACETYSULFANILAMIDE

DOG NO.	WEIGHT (KG.)	DOSE (GM.)	TIME AFTER INITIAL DOSE	MG. OF SULFANILAMIDE PER 100 C.C. OF BLOOD	
				FREE	ACETYLATED
1	15.4	8	30 min.	Trace	3.78
			1 hr.	0.47	7.53
			2 hr.	0.58	12.42
			3 hr.	0.90	17.60
			4 hr.	0.93	14.67
			6 hr.	0.97	12.03
			8 hr.	1.44	10.86
			24 hr.	0.65	1.17
2	20.4	4	30 min.	0.0	1.8
			1 hr.	0.0	2.44
			2 hr.	0.0	4.78
			3 hr.	0.50	6.60
			4 hr.	Trace	6.60
			5 hr.	Trace	7.15
			8 hr.	0.32	5.68
			24 hr.	Trace	1.15

tions made in dogs. The results showing the blood concentrations of sulfanilamide are presented in Table V. Again, small amounts of free sulfanilamide appeared in the blood. The maximum concentration of acetylated sulfanilamide in the blood was reached within the first six hours after receiving a single dose and declined slowly thereafter. Urine was collected over the first twenty-four-hour period for Subjects H. B. and B. N. The urine from Patient H. B. contained 2.95 mg. per 100 c.c. of free sulfanilamide and 57.5 mg. of acetylated sulfanilamide. The

TABLE IV

CONCENTRATIONS OF FREE AND ACETYLATED SULFANILAMIDE IN THE BLOOD AND URINE OF AN ANIMAL RECEIVING DIVIDED DOSES OF ACETYSULFANILAMIDE

DOG NO.	WEIGHT (KG.)	DOSE	TIME AFTER INITIAL DOSE	MG. OF SULFANILAMIDE PER 100 C.C. URINE		MG. OF SULFANILAMIDE PER 100 C.C. BLOOD	
				FREE	ACETYLATED	FREE	ACETYLATED
3	16.3	8 Gm., then 1 every 4 hr.  Total, 13	30 min.	2.20	0.58	Trace	1.12
			1 hr.			Trace	2.47
			2 hr.	3.40	21.30	0.33	2.95
			3 hr.	4.17	52.73	0.40	4.20
			4 hr.	2.57	51.83	0.38	8.92
			6 hr.	2.84	50.46	0.58	12.32
			8 hr.			2.68	13.92
			12 hr.			2.55	18.25
			16 hr.			2.57	16.33
			20 hr.*			2.74	15.16
			24 hr.			3.06	15.44
			28 hr.			2.65	10.25
			32 hr.			2.98	9.82
			36 hr.			2.14	7.06
			48 hr.			1.38	3.42
			56 hr.			1.13	0.49
			72 hr.			0.52	0.84

\*Acetylsulfanilamide discontinued.

peared in the bile than in the blood. This was true for both sulfanilamide and sulfapyridine. Patient J. B. (Table II) had very high concentrations of bile sulfapyridine, with relatively small amounts present as the conjugated form. This patient had a moderately severe systemic reaction following the ingestion of the drug. She had chilly sensations, severe headache, and marked nausea, but no vomiting.

TABLE II  
CONCENTRATION OF SULFAPYRIDINE IN BILE AND BLOOD

PATIENT	DOSE	HOURS AFTER INITIAL DOSE	MG. PER 100 C.C. IN BILE			MG. PER 100 C.C. IN BLOOD		
			FREE	TOTAL	PERCENTAGE ACETYLATED	FREE	TOTAL	PERCENTAGE ACETYLATED
J. B., 55- year-old male	½ Gm., then 1 every ½ hr. Total, 5	4*	5.6	5.8	3.5	8.5	11.2	23.7
		6	38.5	43.5	11.5	11.6	13.6	14.7
		24	51.3	51.3	0.0	17.9	19.6	8.7
		48	6.4	7.9	19.0	3.8	6.2	37.8
F. W., 49- year-old female	½ Gm., then 1 every ½ hr. Total, 5	4*	0.0	0.0	0.0	7.3	11.0	33.7
		6	0.0	0.0	0.0	9.3	12.7	26.8
		24	8.5	9.0	5.6	8.5	12.4	31.4
		48	6.2	6.5	4.6	2.6	4.2	38.2
J. B., 61- year-old male	½ Gm., then 1 every ½ hr. Total, 10	4	0.0	0.0	0.0	3.1	4.0	22.5
		6	5.2	5.4	3.7	4.9	6.4	23.4
		24*	20.4	24.4	16.4	7.6	10.4	26.8
		48	12.6	12.8	1.6	7.4	10.1	26.7

\*Sulfapyridine discontinued.

A culture of *E. coli* was obtained from bile specimens of Patients J. B. and F. W. (Tables I and II) before they received any drug. Following the administration of sulfanilamide, and later following sulfapyridine, this organism was still present in the bile of both patients. It is noted that Patient J. B. had a level of 51.3 mg. of sulfapyridine per 100 c.c. of bile.

When a single, large dose of acetylsulfanilamide was administered orally to dogs, an appreciable concentration of this form of sulfanilamide was attained in the blood (Table III). It is of interest that small amounts of free sulfanilamide appeared in the blood, indicating some degree of hydrolysis of acetylsulfanilamide in the animals' bodies. Table IV shows a larger number of observations made upon a third animal receiving divided doses of acetylsulfanilamide. No toxic manifestations were apparent in any of the dogs. The acetylated form of sulfanilamide was readily recovered from the urine and also free sulfanilamide in smaller quantities. These observations in dogs are in agreement with the previous studies of Marshall and his associates<sup>8</sup> and with those of Ockerblad and Carlson.<sup>9</sup>

Acetylsulfanilamide was then administered orally to three human subjects in order to compare the effects of the drugs with the observa-

TABLE VI  
COMPARATIVE STUDY OF EXCRETION OF SULFANILAMIDE AND ACETYSULFANILAMIDE IN HUMAN BILE

PATIENT	HOURS OF COLLEC- TION	SULFANILAMIDE				ACETYSULFANILAMIDE			
		BLOOD (MG. PER 100 C.C.)		BILE (MG. PER 100 C.C.)		BLOOD (MG. PER 100 C.C.)		BILE (MG. PER 100 C.C.)	
		FREE	CONJUGATED	FREE	CONJUGATED	FREE	CONJUGATED	FREE	CONJUGATED
J. W., 41-year-old female	4 21	7.4 6.53	8.72 7.57	1.4 7.59	0 Trace	Trace Trace	8.4 10.52	Trace 1.51	2.5 2.87
D. J., 74-year-old female	4 20	1.6 8.7	1.0 6.2	Trace 5.2	Trace Trace	1.6 2.0	6.7 11.2	1.8 1.4	1.7 5.4
L. B., 47-year-old female	4 21	4.39 11.3	10.31 8.3	3.40 9.28	Trace Trace	4.4 1.8	8.5 11.1	1.4 1.4	1.9 2.9
A. K., 63-year-old male	4 20	9.1 9.0	3.0 3.5	Trace 3.4	Trace Trace	Trace Trace	2.8 3.78	Trace Trace	Trace 2.36
M. A., 61-year-old female	4 20	6.0 10.2	2.3 5.7	3.1 4.8	Trace Trace	2.0 1.9	6.7 12.3	1.0 1.1	2.9 6.3
B. L., 57-year-old male	4 21	2.6 10.3	1.0 4.0	Trace 7.6	Trace 1.0	Trace Trace	4.3 6.7	Trace Trace	1.2 2.0
H. B., 36-year-old male	4 21	7.1 6.4	2.6 7.9	4.9 5.6	Trace 1.0	Trace 1.2	5.7 7.0	Trace 1.2	Trace 3.1

TABLE V

CONCENTRATIONS OF FREE AND ACETYLATED SULFANILAMIDE IN HUMAN SUBJECTS  
RECEIVING ACETYSULFANILAMIDE

HUMAN SUBJECT	DOSE (gm.)	TIME AFTER INITIAL DOSE	MG. OF FREE SULFANILAMIDE PER 100 C.C. OF BLOOD	MG. OF ACETYLATED SULFANILAMIDE PER 100 C.C. OF BLOOD
W. D., 17-year-old male	4	1.5 hr.	0.248	5.0
		3 hr.	0.291	4.95
		4 hr.	0.216	4.72
		6 hr.	0.458	4.25
H. B., 16-year-old male	6	30 min.	Trace	3.67
		1 hr.	Trace	3.54
		2 hr.	0.44	5.36
		3 hr.	0.42	5.30
		4 hr.	0.53	4.59
		6 hr.	0.47	4.80
		8 hr.	0.36	3.99
		24 hr.	0.36	2.34
		48 hr.	Trace	1.53
		72 hr.	Trace	1.01
		96 hr.	0	0.58
		120 hr.	0	1.18
B. N., 27-year-old female	6	30 min.	Trace	2.17
		1 hr.	Trace	4.70
		3 hr.	0.36	4.79
		4 hr.	0.40	2.42
		6 hr.	0.50	1.60
		8 hr.	0.50	1.70
		24 hr.	0.38	1.02
		48 hr.	Trace	0.44

total amount of sulfanilamide recovered in this period was 1.03 Gm. A twenty-four-hour collection of Patient B. N. had 4.65 mg. per 100 c.c. of free sulfanilamide and 83 mg. of the acetylated form with a total recovery of 1.92 Gm. These observations confirm those of Ockerblad and Carlson.<sup>9</sup> All three individuals tolerated the drug well. Patient B. N. (Table V) complained of a headache several hours after receiving the drug. None showed any evidence of cyanosis, and methemoglobin was not detected spectroscopically in blood samples.

Having established to our own satisfaction that acetylsulfanilamide could be safely administered to human subjects, the compound was given orally to seven individuals having T-tubes in the common duct. They were given a total of 20 Gm. in twenty hours. None of the patients had any appreciable manifestations of toxicity. At another period, these same subjects had received equivalent doses of sulfanilamide and the amounts of free and acetylated sulfanilamide quantitated in the bile and blood. Comparative results, showing the concentrations of free and acetylated sulfanilamide in the bile and blood when sulfanilamide had been administered, and also the results after acetylsulfanilamide had been given, are shown in Table VI. Attention is called to the fact that, following the exhibition of sulfanilamide, only small quantities of the

cholangitis and one case of jaundice with neoprontosil. They did not present the results of this therapy but stated that the drug did not cause any evidence of hepatic damage. Cleveland<sup>14</sup> administered neoprontosil and sulfanilamide to a patient with severe cholangitis, marked liver damage, and jaundice and ascribed recovery of the patient to chemotherapy. Only a few instances are recorded where the sulfonamides have been used in the treatment of patients with biliary typhoid and paratyphoid infections. Bazin<sup>15</sup> had a patient from whom paratyphoid B bacilli were consistently isolated from the bile and feces. He was successful in eradicating the infection with sulfanilamide. On the other hand, Lembcke<sup>16</sup> failed in an attempt to treat a typhoid carrier after apparently adequate doses of sulfanilamide had been used.

Although sulfanilamide and its derivatives may prove useful in the treatment of certain suppurative conditions of the biliary tract, these drugs must be administered cautiously to patients with liver injury.<sup>17</sup> Watson and Spink<sup>18</sup> have observed that a majority of patients receiving the usual therapeutic doses of sulfanilamide had a resultant temporary hepatic dysfunction. They noted that, when the drug was given to patients who had evidence of liver damage before therapy was started, there was an increase in the degree of liver dysfunction coincident with the administration of the drug.

Finally, the colon bacillus is one of the most commonly found microorganisms in suppurative conditions of the biliary tract. In the present study, it was observed that this organism persisted in the bile of two patients even after high concentrations of sulfanilamide and sulfapyridine had been maintained for several days. There are some strains of this organism that are notoriously resistant to the action of sulfanilamide. Therefore, in treating patients who have infections of the biliary tract and hepatic injury with sulfanilamide or its related compounds, one may be faced with the likelihood of failing to affect the infection and at the same time producing further hepatic damage.

#### SUMMARY

1. Sulfanilamide and sulfapyridine were administered to patients several months after performance of a cholecystectomy and choledochostomy, accompanied by T-tube drainage of the common bile duct. This procedure permitted the collection of bile specimens.
2. Appreciable concentrations of sulfanilamide and sulfapyridine were attained in hepatic bile when compared to the blood levels.
3. Lower levels of the conjugated forms were present in the bile than in the blood.
4. Administration of acetylsulfanilamide to human subjects resulted in lower concentrations of this compound in hepatic bile than in blood.
5. The use of the sulfonamide compounds in the treatment of infections of the biliary tract is discussed.

conjugated form of sulfanilamide appeared in the bile as compared to the blood. On the other hand, when acetylsulfanilamide was administered, higher concentrations of this form were present in the bile, but in no instance did it reach the levels present in the blood. It is also apparent that part of the acetylsulfanilamide was hydrolyzed in the body since free sulfanilamide was detected in the blood and bile after acetylsulfanilamide had been administered.

#### DISCUSSION

It may be concluded from the foregoing data that appreciable concentrations of sulfanilamide and sulfapyridine may be obtained in human bile when therapeutic doses are administered orally. Although the number of observations made is small, it is of interest to note the high concentrations of sulfapyridine found in the bile of two individuals as compared to the blood, and yet a higher percentage of the conjugated form was present in blood samples. Marshall and Litchfield<sup>10</sup> have pointed out that, following the administration of sulfapyridine to dogs, higher concentrations of the drug were found in the liver than in the blood. This was not true for sulfanilamide. Since Stewart and his associates<sup>11</sup> observed that over 90 per cent of ingested sulfanilamide may be recovered in the urine; since it has also been found that the kidneys are the main excretory channel for absorbed sulfapyridine,<sup>12</sup> it is not unlikely that, after the compounds are excreted in the bile, they are reabsorbed to a considerable extent from the intestinal tract.

This study has brought forth further information concerning the excretion of these compounds. It is now generally agreed that at least partial acetylation of sulfanilamide and sulfapyridine takes place in the liver. The present observations reveal that lower concentrations of the conjugated products are found in the bile than in the blood, even when pre-formed acetylated sulfanilamide is brought to the liver. It would appear that acetylation is a protective phenomenon whereby the organism attempts to convert a toxic substance into one which, though not less toxic, is more readily eliminated through the kidneys. Conjugated sulfanilamide and sulfapyridine are cleared more rapidly through the kidneys than the free forms.<sup>11, 12</sup>

Since appreciable levels of sulfonamide compounds may be obtained in the bile when administered orally or parenterally, it would be anticipated that the drugs would be of value in the treatment of infections of the biliary tract. A few clinical reports bear this out and in a few instances we have noted striking improvement following the administration of sulfapyridine. Manche, Plotner, and Siede<sup>1</sup> successfully utilized prontosil and neoprontosil in the treatment of patients with cholangitis, cholecystitis, and hepatitis. Some of their patients were jaundiced before therapy was instituted. Herrell and Brown<sup>13</sup> treated two cases of

# THE VALUE OF THE LOCAL IMPLANTATION OF CRYSTALLINE SULFANILAMIDE ABOUT GASTROINTESTINAL ANASTOMOSES IN DOGS\*

A VALUABLE ADJUNCT IN THE PREVENTION OF PERITONITIS

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FOR THE PAST two years studies have been in progress upon the physiology of gastric secretion at the Experimental Laboratory, Department of Surgery, University of Minnesota. During the process of these investigations more than 250 operations were performed upon the gastrointestinal tract of the dog. Despite the development of a method<sup>1</sup> of closed gastrojejunal anastomosis, which in the clinic was accompanied by a mortality of less than 2 per cent for gastric resections for ulcer and less than 10 per cent for gastric resections for carcinoma, the procedure on the dog was by no means so successful. The mortality in the dog, accompanying complicated gastrojejunal anastomosis, was surprising in the light of the relatively low mortality after gastrojejunal anastomosis employing the closed technique in man.

On looking into the literature, it was observed that Martzloff and his associates<sup>2</sup> found that leakage was present in 7 to 10 per cent of the end-to-end small bowel anastomosis made with silk in the dog, using their modification of a closed technique. Similarly executed procedures utilizing a running catgut stitch developed leakage in 25 per cent of the cases. In the Mann-Williamson operation, known as "duodenal drainage" the duodenum, severed from the pylorus and jejunum but receiving all biliary and pancreatic secretions, is anastomosed to the lower small intestine and continuity of the intestine is re-established by gastrojejunostomy. Markowitz<sup>3</sup> states that performance of this operation in dogs with a mortality of 20 per cent indicates a mastery of the technique of intestinal anastomosis. Such a figure is hardly acceptable for even the more complicated intestinal procedures in man.

Intestinal surgery is more difficult in the dog because the lumen is smaller and the gut wall thicker and more friable. Too, attempts at avoiding leakage by broad approximation of a cuff about an anastomosis readily leads to stenosis or obliteration of the lumen by the diaphragm produced. In our experience, we have found that the importance of all of these factors is pyramided by the relatively decreased resistance of dogs to peritoneal insults.

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during an anastomotic procedure. Operations were executed with surgical asepsis under ether anesthesia. The skin was shaved, cleansed with soap and water, and prepared with Novak's solution.<sup>8</sup> The operator and assistants wore caps, masks, sterile gowns, and rubber gloves. Interrupted fine silk sutures\* were employed almost exclusively in construction of a closed type of anastomosis made according to the Wangensteen<sup>9</sup> technique. After completion of the operation suture lines were carefully inspected, and just prior to closure of the abdominal wall and peritoneum, crystalline sulfanilamide was dusted liberally about the anastomosis, the total amount not exceeding 5 Gm. Adequate parenteral fluids of normal saline solution were administered for the following three days. Liquids were allowed first sparingly after this period, and solid foods were added to the diet on the eighth postoperative day.

### RESULTS

The results following adoption of this plan have been summarized in Table I.

There were two deaths from pneumonia on the first and seventeenth postoperative days and one from gastroenteritis on the fourteenth day in this series. At post-mortem in each instance an unusually heavy deposit of fibrin firmly sealed the serosal surfaces at every suture line. Elsewhere the peritoneum was smooth and glistening. With a mechanism for inhibiting bacterial growth locally, normal post-operative healing promptly took place. The rapidity of this process was strikingly apparent in the dog dying during the first twenty-four hours from a regurgitation pneumonia. In animals dying at this interval of generalized peritonitis, there is little fibrin sealing the anastomotic sites and the stitch holes themselves leak contamination.

Markowitz,<sup>4</sup> quoting Saint, suggests that end-to-end anastomosis of the esophagus is difficult and often meets with failure because of the poor blood supply, the constant movement to which it is subjected, the encroachment on mediastinal structures and danger of infections spreading into fascial planes, and absence of serosa or a greater omentum with which to seal anastomotic lines. In the hands of an experienced operator, employing a specialized technique and with preliminary phrenicotomy, the mortality is said to approximate 20 per cent.<sup>5</sup> Rea<sup>10</sup> and Dragstedt and Mullenix<sup>11</sup> noted a high incidence of fatal mediastinitis after single-stage esophagostomy. On a similar basis clinical experience favors the two-stage procedure for esophageal diverticula. This operation, therefore, seemed to offer a very fundamental test of the ability of the drug to allow a fibrin seal to develop about anastomotic lines, despite bacterial contamination. Three end-to-end anastomoses were made at the level of the cervical esophagus and two anastomoses completed at the end of the esophagus to the duodenum without

\*Individual Champion No. 1 silk sutures are threaded on Anchor brand, stainless steel, round-point No. 1 eye needles.

No comprehensive bacteriologic investigations have been made of cultures obtained from mucosal surfaces about either the closed, aseptic type or open anastomoses. The regular diet fed our animals remained in their stomachs often for prolonged periods so that occasionally, despite precautionary measures, an alimentary residue with its bacterial content augmented contamination at the operative site.

Frequently dogs would succumb to a generalized peritonitis thirty-six to forty-eight hours after establishment of an anastomosis which seemed quite satisfactory from every point of view at completion of the operation. This experience was discouraging, to say the least. A careful study of peritonitis leads one not into its treatment but toward its prevention. Fortunately, in the majority of the cases of peritonitis following gastrointestinal surgery, there is an interval between the onset and an irreversible stage. This period varies with different circumstances; i.e., the amount of contamination and duration of its activity, virulence of the bacterial organisms, resistance of the host, and other less well-known factors. Consistently successful operations required interruption of this cycle by thwarting such potential infection. Chemotherapy appeared to offer this means. Garlock and Seeley<sup>6</sup> had pointed out the value of giving 0.8 per cent sulfanilamide as an isotonic solution subcutaneously in the prophylaxis of peritonitis after colonic surgery. Every eight hours 500 c.c. of 0.8 per cent sulfanilamide solution was given subcutaneously to four dogs upon which a type of duodenal drainage operation had been performed. Three of these animals died of generalized peritonitis. This method of administering the sulfanilamide apparently gave the animals but slight protection. Having in mind the nice results obtained by Jensen and his associates<sup>7</sup> with the local implantation of crystalline sulfanilamide in compound fractures, it was, therefore, proposed to place the drug about the suture lines at the time of operation. This represented the sole modification of our former technique. Results were even better than had been anticipated, for a series of thirty-seven operations were performed without a death from peritonitis. The experience gained with local implantation of sulfanilamide about the suture lines in gastrointestinal anastomoses of varying complexity constitutes the subject of this paper.

#### METHOD AND MATERIALS

Young adult mongrel dogs weighing between 15 and 25 kg. were secured and fed well for several days prior to operation. All animals were prepared during the twenty-four-hour period before surgery. One pound of raw hamburger or horse meat and water were allowed the night before the operation, but all other food was withheld from the diet. This plan usually provided a collapsed stomach and upper intestinal tract free of partially digested material, thereby lessening the danger from accidental spillage of contaminated intestinal contents

a failure or death. All of these were performed with the clamp or closed method and crystalline sulfanilamide was deposited about the suture line.

In three animals there was a single-stage interposition of the ileocecal valve between the pylorus and duodenum to reduce regurgitation of alkaline intestinal juices after the manner of Dragstedt's mechanical valve. This operation entails a gastroileostomy, coloduodenostomy, and ileocolostomy. One death occurred in this group on the seventeenth postoperative day from pneumonia. At autopsy the peritoneal surfaces were smooth and glistening, and all suture lines were sealed by an organized deposit of fibrin.

#### DETERMINATION OF SULFANILAMIDE BLOOD LEVELS

Blood levels, employing the method of Bratten and Marshall,<sup>13</sup> for sulfanilamide implanted intraperitoneally or injected subcutaneously in isotonic solution, were determined in a group of control dogs not in the operated series of Table I. Samples were obtained in duplicate each fifteen minutes for the first hour and hourly for twenty-four to thirty-six hours thereafter.

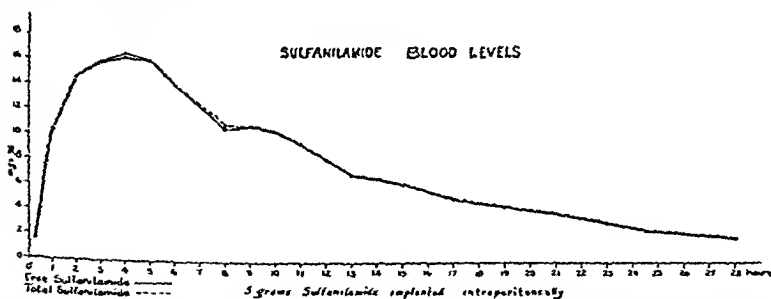


Fig. 1.—There is a prompt rise in the blood level of sulfanilamide, reaching a maximum value in three hours, sustained but a short while, and elimination is nearly complete in twenty-four hours. The values for free and total sulfanilamide check closely since dogs do not acetylate this drug.

The values obtained for blood sulfanilamide following the local implantation of the crystalline form of the drug intra-abdominally are lower than those obtained following the subcutaneous administration of a similar amount in an isotonic solution. A reasonable explanation by analogy for the failure of sulfanilamide in solution to protect against peritonitis is noted in the experiments of Jensen and his co-workers. They pointed out that sulfanilamide placed other than at the site of experimentally produced compound fractures was unable to prevent local infection at the fracture site.\* Blood levels for sulfanilamide appear to be less important for the production of local bacteriostasis than the actual concentration of the drug at the site of contamination. In the

\*The recent work of Hawking<sup>14</sup> supports this viewpoint. Local application of sulfonamides was found to be significantly superior to systemic treatment with these drugs in protecting against *Clostridium welchii* and *Cl. septicum*.

TABLE I

OPERATIVE PROCEDURES COUPLED WITH LOCAL IMPLANTATION OF CRYSTALLINE SULFANILAMIDE (5 GM. OR LESS) ABOUT ALL SUTURE LINES AND COMPARABLE OPERATIONS COMPLETED WITHOUT SULFANILAMIDE

PROCEDURE	SULFANILAMIDE IMPLANTED			SULFANILAMIDE NOT IMPLANTED		
	NO. OF DOGS	PERITONITIS	OTHER CAUSES	NO. OF DOGS	PERITONITIS	OTHER CAUSES
Heidenhain gastric pouches	9	0	0	39	10	14
Pavlov pouches	2	0	0	41	13	16
Antral exclusion (or resection) and gastrojejunostomy (side-to-side)	2	0	0	16	3	0
Pyloric gastrojejunostomy (end-to-side)	7	0	0	14†	2	2
Gastrooduodenostomy (side-to-side)	6	0	1	5	2	0
Jejunum resection and jejunojejunostomy (side-to-side)	1	0	0			
Esophagoduodenostomy (end-to-side) total gastric pouch or total gastrectomy	2	0	0			
Resection with end-to-end anastomosis of cervical esophagus	3	0	0			
Pyloric gastrolleostomy (end-to-side)						
Coloduodenostomy (side-to-side)						
Ileocolostomy (side-to-side)*	3	0	1			
Ileocolostomy (side-to-side)	1	0	0			
Pyloric gastrolleostomy (end-to-side)						
Coloduodenostomy (side-to-side)*						
Subtotal gastric pouches	1	0	1			
Jejunojejunostomy (side-to-side) and gastrojejunostomy (side-to-side)				17	8	7
				16	6	5
Totals	37	0	3	148	44	44

\*In this operation the ileocecal valve is interposed isoperistaltically between the pylorus and the duodenum to reduce the intragastric reflux of bile and pancreatic juices after the manner of Dragstedt's mechanical valve.

†Gastrojejunostomy (side-to-side).

Cyanosis and jaundice were rare. Unlike man, the dog fails to acetylate sulfanilamide circulating in its blood stream so that values for free and total sulfanilamide check closely, and, therefore, the amount available from a single dose may be even 20 per cent more than man would utilize from the same amount of the drug. In addition, recalling the great disparity of weight between man and dog, the canine tolerance appears even more manifest. In man acetylation is a detoxification process, a probable further indication of a decreased tolerance as contrasted with dogs.

Clinical application of this work has been cautiously expanded since so little is known of man's ability to assimilate safely the sulfanilamide so rapidly absorbed following its implantation intra-abdominally in the crystalline form. In this respect, Watson and Spink<sup>12</sup> have pointed out that mild liver damage secondary to toxic drainage from intra-peritoneal sepsis via the portal circulation can be converted into outspoken hepatic dysfunction characterized by urobilinogenuria, elevation of serum bilirubin, and jaundice by the administration of therapeutic doses of sulfanilamide.\*

In instances of operation for colonic resection with primary anastomosis at the University of Minnesota Hospitals, usually 2 or 3 Gm. of sulfanilamide† are implanted about the suture lines, and an additional 1 Gm. is distributed over the wound edges of the abdominal wall above the peritoneum during closure. The use of sulfanilamide has been limited in gastric resections to those cases with perforation onto an adjacent viscus; i.e., a pancreas into which a contaminated site must be opened.

The efficacy of implanting crystalline sulfanilamide about colonic anastomosis in man on the indications stated above has been difficult to evaluate. The adoption of the closed method of anastomosis has made resection with primary anastomosis, wherever feasible, the method of choice in surgery of the colon. Large, fixed lesions have been removed under trying circumstances and anastomosis made with surprisingly low operative risk. The risk of primary colon resections from the University Hospital experience would appear to be about 5 per cent. If sulfanilamide could be embedded in a vehicle which would permit gradual liberation of the drug over a prolonged period, the bacteriostatic effect of local implantation would be enhanced greatly. Whether the local implantation of sulfanilamide will make such anastomosis even safer remains to be determined. Mindful of the great protective value of the method in the dog in preventing the lysis of fibrin and in encouraging early agglutination of the approximated serosal surfaces, it

\*Investigation is now in progress on a method of combining the sulfanilamide with a vehicle so as to maintain a prolonged local action and to produce a delayed rate of absorption into the circulation.

†Sulfathiazole has been used more often recently.

case of local implantation this value probably approximates the solubility of the drug in tissue fluid (*circa* 0.8 per cent), or fifty times the ordinary blood level. It was noted during the process of these determinations that dogs tolerate well relatively high blood levels of sulfanilamide and exhibit few of the symptoms manifested clinically. Apathy and anorexia did occur with large doses given by mouth.

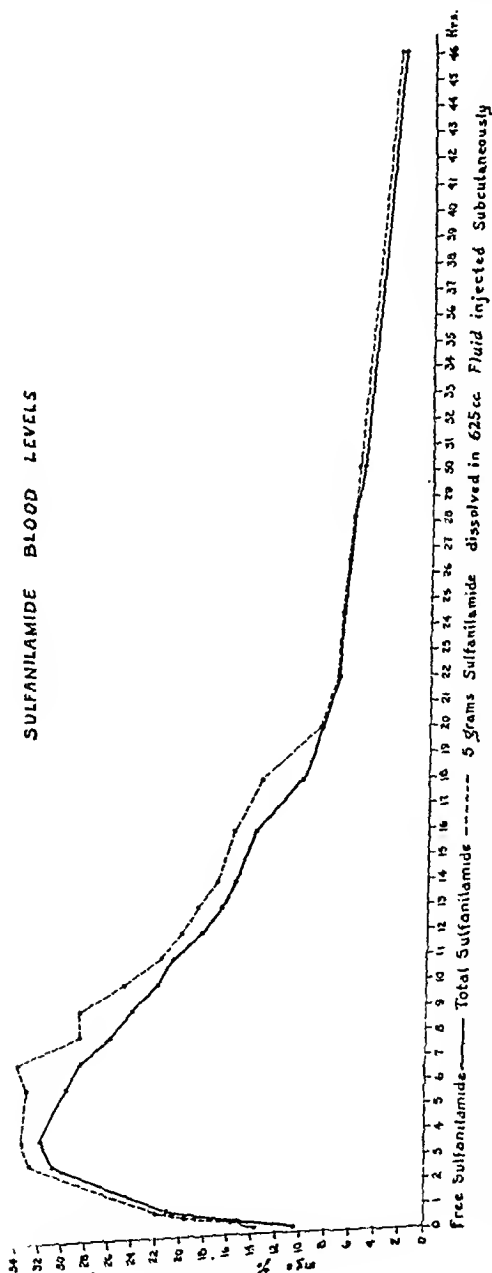


Fig. 2.—The blood levels for sulfanilamide obtained after subcutaneous administration of the drug in 0.8 per cent solution are substantially higher than those noted following intraperitoneal implantation of a similar amount in the crystalline form.

# PERITONEAL VACCINATION, IRRIGATION, AND CHEMOTHERAPY IN THE TREATMENT OF EXPERIMENTAL PERITONITIS

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IN THE PAST much of the experimental and clinical work of peritonitis has been concerned with its prevention during accompanying gastrointestinal disease and gastrointestinal surgery or with the treatment of altered physiologic functions that arise during the disease. The epochal contributions toward a better understanding of distention, shock, and fluid requirements of this disease have done much to reduce the mortality. Nevertheless, therapeutic measures combating the etiological bacteria of this disease should always receive first consideration.

Bacterial peritonitis is usually due to perforation secondary to other disease of the gastrointestinal tract. The resulting bacterial flora is accordingly diverse. Altmeier<sup>1</sup> in an extensive review and from personal observations and similarly Bowers and associates<sup>2</sup> and Meleney and co-workers<sup>3</sup> have emphasized this diverse bacterial flora. Altmeier also concluded from his studies that it was impossible to predict the course of appendical peritonitis from the kind of bacteria isolated in any one case, but that those patients with only a single bacterial type of culture usually survive the disease.

Bacteriologic studies were done at the time of death on the peritoneal exudates of 15 dogs by means of direct smears and aerobic and anaerobic cultures, with complete identification of the organisms. In 4 dogs with cecal perforation, direct smears showed gram-negative bacilli, streptococci, gram-positive spore formers, and very few diphtheroids. Aerobic cultures showed *Bacillus coli* and *Streptococcus viridans* (enterococcus). Anaerobic cultures showed the above organisms plus *B. welchii*.

In the 11 dogs with ileal perforation, gram stain showed numerous small gram-negative bacilli, many gram-positive spore formers, streptococci and occasional gram-positive diplococci. Aerobic cultures showed in all instances *B. coli* and *Str. viridans*. In 3 of the 11 cases cultures also showed *Staphylococcus albus*, *B. proteus*, *B. aerogenes*, and a gram-negative motile bacillus of the *Salmonella* group. Occasionally diphtheroids and mucoid variants of *B. coli communis* were cultured. Anaerobic cultures showed *B. welchii* plus the above organisms.

\*Bacteriological work done by Dr. Edward Birge, of the Wisconsin State Laboratory of Hygiene.

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is reasonable to believe that local implantation of crystalline sulfanilamide or allied chemotherapeutic agents may prove a worth-while adjunct to the closed anastomosis in man.

Experimentally the local implantation of crystalline sulfanilamide about gastrointestinal suture lines in dogs appears to promote healing by inducing local bacteriostasis and inhibition of fibrinolysis. This mechanism is an aid in preventing peritonitis. Clinical evaluation of its worth requires additional trial.

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suspension of formalized colon bacilli in gum tragacanth and aleuronat. This agent increases the local peritoneal resistance and its action is nonspecific, for the protection is not limited solely to *B. coli*, but it also affords protection against other bacilli. Other agents have been used but apparently this colon bacillus suspension is the most effective one.<sup>8</sup>

In 6 dogs 7.5 to 20 c.c. of coli baetragen, depending on the size of the dog (1 to 1.5 c.c. per kilogram), was injected intraperitoneally prior to opening the distal ileum. Six dogs were used, of which 2 were injected twenty-four hours, 2 forty-eight hours, and 2 seventy-two hours before the operation. All dogs lived. Laparotomy a month later showed many fibrous peritoneal adhesions and a scar at the site of the ileal opening 0.5 to 0.75 cm. in length.

In further work coli baetragen was injected intraperitoneally in 6 dogs six hours before opening the ileum. Two of these dogs died and necropsy revealed a generalized peritonitis with many adhesions and a partial closure of the ileal opening. The surviving dogs on exploratory laparotomy three months postoperatively showed numerous fibrous peritoneal adhesions and a scar at the site of the ileal opening.

In 3 dogs coli baetragen was injected at the time the ileum was opened and all dogs died within forty-eight hours. Autopsy revealed a sanguinous exudate, a few fine adhesions, but no attempt at closure of ileal opening.

Coli baetragen was then given intraperitoneally to 5 dogs, 1 of which was injected simultaneously with one billion *B. coli* in 2 per cent gum tragacanth per kilogram of body weight; 2 were injected with *B. coli* in twenty-four hours and 2 forty-eight hours after the administration of Coli baetragen. The first dog died and all the others survived. At autopsy a large amount of serosanguineous exudate was present in the peritoneal cavity and there were only a few adhesions. Exploratory laparotomy on the other dogs showed no adhesions and peritoneal surfaces were smooth and glistening.

Peritoneal irrigation in the treatment or prophylaxis of peritonitis is one of the older therapeutic procedures. French and German surgeons often wash out the peritoneal cavity with liberal amounts of water or saline solution before closure of each laparotomy as a prophylactic measure and also use this as a therapeutic procedure. Taue and Trzebiak<sup>9</sup> employed antiseptic solutions as peritoneal irrigants and noted some improvement over controls. One of the most recent reports, that of Behan,<sup>10</sup> speaks favorably of alcohol peritoneal lavage at time of surgery in the presence of peritonitis. In our work saline sodium ricinoleate (soricin) and zephiran\* were used. In 2 dogs immediately following ileal perforation 10,000 c.c. of normal saline solution as a continuous peritoneal irrigation was used and both dogs died. At autopsy no adhesions were found and peritoneal fluid was markedly hemorrhagic.

\*Material made available through the courtesy of Alba Pharmaceutical Company.

These studies would tend to demonstrate that the same flora of organisms exists in the peritoneal cavity as is normally present in the lower ileum and cecum. Of interest was the observation that there was a marked paucity of organisms in the smears made from exudates of cecal perforation as compared to those made from exudates of ileal perforation.

In our experimental work we hoped first to determine the effectiveness of peritoneal vaccination toward subsequent peritonitis, and second to determine the therapeutic efficacy of peritoneal irrigations and chemotherapy in peritonitis. All this work was done upon dogs weighing more than 7.5 kg. No dog had any previous abdominal surgery and all operative procedures were done under open-drop ether anesthesia with morphine sulfate  $1\frac{1}{2}$  to 2 gr. two hours before operation.

In order to obtain a control series, we first attempted the production of perforating lesions in the cecal pouch of dogs. In 6 dogs the arterial supply to the cecal area was ligated and 3 dogs died. In 5 dogs, in addition to the arterial ligation, the corresponding cecum was crushed with hemostats for ten to thirteen minutes. Two of these dogs died. In 5 dogs a 1 cm. opening was made into the cecum and only 1 of these dogs died. It is seen that none of these procedures carried a mortality of over 50 per cent.

In an endeavor to increase this mortality, virulent *B. coli* (750 million per kilogram), obtained from a fatal case of peritonitis in a dog, were given intraperitoneally in saline solution to 3 dogs, and all lived; and in a 2 per per gum tragacanth suspension to 4 dogs and again all lived. One billion *B. coli* (No. 300 from Dr. B. Steinberg) (per kilogram) suspended in gum tragacanth given intraperitoneally in 6 dogs produced death in all cases in thirty-six hours.

To obtain a more diverse bacterial flora in peritonitis, we followed the methods of Okada<sup>4</sup> and of Bergh, Bowers, and Wangenstein<sup>5</sup> and made a 1 cm. opening in the ileum 8 cm. from the ileocecal junction. Of 15 dogs, 14 died, a mortality of 93.33 per cent. Ten dogs died of generalized peritonitis within forty-eight hours, and autopsy demonstrated the presence of a serosanguineous exudate and no adhesions. Three dogs died between seventy-two and ninety-six hours after surgery, and necropsy revealed numerous adhesions and occasional small abscesses. One dog survived three weeks and died after the apparent intraperitoneal rupture of a large abscess. The surviving dog on later exploration demonstrated a complete closure of the ileal perforation by adhesions to adjacent loops of bowel and omentum. This group of fifteen dogs served as our main control series.

Peritoneal vaccination, a prophylactic procedure against peritonitis according to the work of Steinberg and Goldblatt,<sup>6, 7</sup> has been used when peritoneal contamination is likely to occur during or after gastrointestinal surgery. The commonly used antigen is coli bacitracin,\* a

\*Made available through the courtesy of Dr. B. Steinberg.

third postoperative day and no peritoneal exudate was found. The serosa was smooth, injected, and the ileal opening was covered by omentum.

Neoprontosil was then given to 4 dogs, with the first injection given four hours after the operation. One dog died, a mortality of 25 per cent. Autopsy revealed extensive fibrinous adhesions and very little exudate. Subsequent exploratory laparotomy on the 3 living dogs revealed minimal fibrous adhesions in 1 and dense adhesions in 2. On the third day blood samples from the dogs that survived showed only a trace of neoprontosil during the period of treatment.

In 6 dogs neoprontosil was begun eight hours after the ileum was opened and 50 per cent of this group died. Post-mortem findings were the same as in the immediately preceding fatal group. One of the surviving dogs was sacrificed on the fourth day and only a trace of neoprontosil was found in 10 c.c. of viscid purulent peritoneal fluid. The ileal opening was closed and there were extensive peritoneal adhesions. Blood samples in the surviving dogs again showed only a trace of neoprontosil.

Five dogs were then given the initial dose of neoprontosil sixteen hours after the operation. Three dogs died within thirty-six hours. Autopsy revealed a large amount of sanguineous fluid and few fibrinous adhesions. Two dogs died seventy-two hours postoperatively and autopsy showed very little exudate but numerous adhesions.

Three dogs were treated solely by inserting 3 to 5 Gm. of sulfanilamide powder into the peritoneal cavity at the time the ileum was perforated. Two of these dogs died, a mortality of 66.66 per cent. Death occurred seventy-two hours postoperatively and autopsy showed many adhesions and a moderate amount of pus.

A solution of 0.5 per cent sulfanilamide was introduced intraperitoneally in 4 dogs at the time the ileum was perforated. Two of the dogs were given 250 c.c. of the solution; the remaining 2, 500 c.c. All dogs died within forty-eight hours and showed at autopsy a large amount of sanguineous peritoneal fluid and few adhesions.

Promine\* was the last chemotherapeutic agent tried. A 1 cm. opening was made in the ileum in 8 dogs and 1 Gm. promine injected intravenously at the conclusion of the operation. The subsequent injections of 1 Gm. promine were given intramuscularly as follows: t.i.d. the same day, t.i.d. the second to fourth days, and b.i.d. the fifth and sixth days. Of this group, 75 per cent survived. Necropsy findings on the 2 fatalities showed partial closure of the ileal opening, 50 c.c. and 200 c.c. of pus, and marked adhesions. Exploratory laparotomy on the surviving dogs revealed minimal adhesions in 2, moderate adhesions in 1, and marked adhesions in 3.

\*Experimental material made available through the courtesy of Parke-Davis and Company.

In 4 dogs zephiran (alkyl-dimethyl-benzol ammonium chloride) irrigations were employed. In 2 dogs immediately following ileal perforation 5 liters of a 1:10,000 solution were used and both dogs died within thirty hours. Two other dogs were irrigated with a 1:20,000 solution with similar results. Autopsy findings were the same as with saline irrigations. In 4 dogs 20 c.c. of 1 per cent sodium ricinoleate solution (soricin\*) as a sclerosing solution was placed into the peritoneal cavity after ileal perforations. All dogs died within seventy-two hours. At necropsy some adhesions were present, but the ileal perforations were not closed.

Neoprontosil was chosen as a chemotherapeutic agent in most of our work because of its ease of administration. Bowers, Burns, and Mengle<sup>11</sup> reported beneficial effects with prontosil in spreading peritonitis in dogs; and Cooper, Gross, and Lewis<sup>12</sup> felt that sulfanilamide was of value in *B. coli* and *B. proteus* peritonitis in mice, but they noted no effect with *B. pyocyaneus* peritoneal infections. As a prophylactic measure Garlock and Seeley<sup>13</sup> in a preliminary report felt that it decreased their incidence of peritonitis following intestinal resections and they were impressed by the smooth uncomplicated convalescence of their patients.

Neoprontosil was given to 16 dogs immediately after the ileum was opened. Therapy consisted of intramuscular injection of 7.5 c.c. q.i.d. the first day, 7.5 c.c. t.i.d. the second to fourth days, and 7.5 c.c. b.i.d. on the fifth and sixth days. Four dogs died, a mortality of 25 per cent. Autopsy upon these revealed definite attempts at closure of the perforation in all cases. Only a small amount of peritoneal fluid was present. Exploratory laparotomy upon the 12 surviving dogs five to seven weeks postoperatively revealed a minimal number of fine adhesions in 4 dogs, a moderate number in 3 dogs, and dense adhesions in 5 dogs. In 3 of the 12 living dogs blood samples on the third day showed only a trace of the drug.

In addition, blood sulfanilamide determinations were carried out on 5 more dogs. These dogs received the same dosage of sulfanilamide as did those in the preceding experiment. Two dogs were used as controls and 3 had openings made in the ileum. Blood specimens were taken one hour and three hours after the second injection each day and in every case only a trace of sulfanilamide was found. The peritoneal exudate obtained from one of the dogs with ileal perforation on the first postoperative day showed 1.8 mg. per cent sulfanilamide. A second dog with ileal perforation was sacrificed on the second postoperative day and the peritoneal exudate showed a trace of sulfanilamide. The third dog with ileal perforation was explored on the

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## DISCUSSION

In our work we were able in a small group of dogs to confirm the work of Schmidt and Taylor<sup>14</sup> and Bergh, Bowers, and Wangenstein that it is practically impossible to obtain a mortality of over 50 per cent in peritonitis induced by perforation or gangrene of the cecum. However, perforation of the distal ileum as reported by the latter workers produced a 100 per cent mortality, and our experience closely approached this with 93.33 per cent fatality. This method brings about a peritonitis with a diverse bacterial flora such as is seen in human beings following gastrointestinal perforation. The high mortality rate provides a basis for the estimation of therapeutic or prophylactic procedures.

Peritoneal vaccination (with coli bactragen) in dogs prior to the operative production of ileal perforation protects against subsequent peritonitis. Apparently it should be given twenty-four to seventy-two hours before the operative procedure. This protection agrees with the result of other workers.<sup>15, 16, 17</sup> The vaccine produces a sterile peritoneal exudate rich in phagocytes which combats an infection in its early stages and subjugates it before an overwhelming bacterial growth occurs. Local tissue changes, such as edema and congestion, also prevent marked bacterial tissue invasion. The inflammatory defensive mechanism is a stage ahead of the bacterial offense following vaccination.

It appears that peritoneal irrigations have no value either mechanically or chemically in the treatment or prevention of peritonitis. The peritoneal washings do not reach all surfaces and remove protective agents in the exudate as well as any bacteria or their toxins. Those bacteria or bacterial toxins that have invaded tissues or lymphatic and hematogenous channels are not reached by the irrigations. We also know from some previous work in our laboratory that continuous peritoneal lavage is shocking and often results in death, even in an unaffected peritoneal cavity.

Sulfanilamide, neoprontosil, promine, and related drugs have been shown<sup>18, 19</sup> to be bacteriostatic and thereby permit the physiologic immunity reactions to combat the invading bacteria. The drugs are most effective against certain hemolytic streptococci, *B. coli*,<sup>12</sup> and *B. welchii*; the last two organisms are most common in any case of peritonitis following gastrointestinal perforation. As is generally agreed and as shown in our work, the earlier in the course of an infection the drug is given the better are the results. The low level of blood sulfanilamide in our dogs suggests that the drug is rapidly excreted and that a larger number of injections may be even more effective.

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and the wounds were impregnated with sulfanilamide crystals when first seen. The patients were then sent back to the field or base hospital, and a thorough débridement was done, the wound being redusted with powder many hours later. The final treatment carried out was irrigation, débridement, packing with sulfanilamide powder, and immobilization of the part. It is known that the powder is soluble in serum and penetrates the fissures of the wound and ragged edges to a great extent. An air pump with a flask and a sterile tip of glass was used to force the powder into the crevices of the laceration. The powder acts in the serum as well as by absorption into the blood stream and lymphatics. Varying lengths and sizes of crayons compressed of the powder and containing 20 Gm., were used, being pushed into bullet wounds. The absorption is much slower in this method. Collapsible tubes of the emulsion of sulfanilamide are being used at the present time in France. The question has arisen of the sterility of the powder. It first was autoclaved, which, it was found, broke it up into its chemical components, often dissolving it into a brown liquid. Since then it has been used in stock bottles which are sterilized by the heat flame or alcohol on the outside and into which it is poured, just as sterile saline solutions are into sterile containers for handling and for use in the surgical team. One of us (J. G. D.)<sup>6</sup> has called attention to the use of the powder as an adjunct in the treatment of peritonitis and the other (L. W. L.),<sup>7</sup> to the use of the powder as an aid in the treatment of breast resections, appendiceal and pelvic abscesses, pyelitis complicating surgical diseases of the abdomen, and local infections, lacerations, and compound fractures and injuries.

#### USES

The typical use of sulfanilamide crystals is divided into office and hospital use.

*Office Use.*—The types of cases treated in the office are those of local infections, small lacerations, boils and abscesses, and the lesser types of injuries in which powder is placed in the wound and sewed up without drainage. If the infection and injury seem to be serious enough, sulfanilamide is given by mouth in addition to the local use. Where the ointment is indicated in office treatments, we use equal parts of sulfanilamide crystals and lanolin thoroughly mixed, preferring the anhydrous type of sulfanilamide ointment because it seems to be more readily absorbable than that placed in petrolatum.

*Hospital Use.*—Hospital treatment consists of: (1) *Crushing and lacerated injuries*, in which the wound is thoroughly débrided, after scrubbing, and preparation of the area, and dusted with sulfanilamide powder, being closed without drainage. (2) *Compound fractures*, in which the patient is treated for shock, after which there is thorough preparation of the injured part with soap and quantities of sterile water, débridement, apposition of the fractured extremity, and, if the fractures

## THE LOCAL USE OF SULFANILAMIDE

LAWRENCE W. LONG, M.D., AND J. GORDON DEES, M.D., JACKSON, MISS.

### INTRODUCTION

THE subject of the application of sulfanilamide crystals to wounds of the body made by trauma or by the surgeon is a subject which is growing in importance, particularly with the vast number of casualties that are appearing in the present war as well as the increasing number of auto accidents. This method is becoming more common in use throughout the world and seems to be a timely one for discussion at this moment. Sulfanilamide is used because it is more soluble than sulfapyridine or sulfathiazol. Its concentration in the blood shows that it is picked up more rapidly than the other two of this group.

### HISTORY

The first material was published by Jensen and co-workers in SURGERY in 1939. Our attention was directed to it by Key<sup>2</sup> in November, 1939, at Memphis, during a meeting of the Southern Medical Association. These authors had made a study of its use in compound fractures after thorough débridement. They did quite an extensive amount of experimental work on rabbits and other animals and found very little, if any, delay in union from the use of this crystalline material in and around the site of the fracture. It was used both with and without the oral administration of the drug with good results. No infections were encountered in their cases. Russell and Falconer<sup>4</sup> (1940) showed that the local application to the rabbit's brain does not cause any appreciable damage to the tissue. However, due to the brain's being encased in a solid vault, there was some mechanical disturbance and it was advised to use the solution if possible. Colebrook<sup>5</sup> (1940) called attention to the experiment done by Legroux of Paris, in the Academy of Surgery. This experiment was carried out on guinea pigs. The abductor muscle was crushed and a small piece of gauze with *Streptococcus hemolyticus* and B. C. Welchii gas bacillus organism was inserted. The gas bacillus is amenable to the sulfanilamide but not so susceptible as the streptococcus. The control pigs died in from two to three days. Those in which the wound was dusted with sulfanilamide powder before closure died in from four to seven days, but, if the wound was opened on the second day and the infected gauze removed and the wound dusted with sulfanilamide, they recovered without débridement. During the present war the English and French surgeons in France and Belgium were instructed to give the wounded patients 2 Gm. of sulfanilamide by mouth

have progressed satisfactorily without infection and the large raw area has offered great absorbent powers as will be shown in Tables I-V on the rate of absorption. One patient with frank acute appendicitis with bilateral pyelitis complicating the disease had 20 Gm. of sulfanilamide powder placed in the peritoneal cavity which cured her pyelitis without further administration of the drug. (5) *Appendical and pelvic abscesses*, which have been treated most successfully without drainage by incising and irrigating the abscessed cavity, placing 20 to 30 Gm. of sulfanilamide powder into the abscess, and closing the abdomen without drain-

TABLE III  
APPENDICAL ABSCESS (15 GM. SULFANILAMIDE POWDER)

1st postoperative day	1.9 mg.
2nd postoperative day	1.4 mg.
3rd postoperative day	0.51 mg.
4th postoperative day	0.41 mg.
5th postoperative day	0.09 mg.
6th postoperative day	0.03 mg.
7th postoperative day	Negative; patient discharged from the hospital

age. The rate of absorption from such walled-off cavities is much slower than in fresh denuded areas or in the peritoneum itself. (6) *Peritonitis*, which locally following acute appendicitis has been treated successfully without any deaths by dusting the sulfanilamide powder into the peritoneal cavity, and which generally has been treated with sulfanilamide in the peritoneal cavity with drainage with marked success. One of us (J. G. D.)<sup>a</sup> reported 1 death in twenty-five cases of perforated appendicitis with peritonitis in which this drug was used. Since that time

TABLE IV  
GENERAL PERITONITIS (15 GM. SULFANILAMIDE POWDER)

1st postoperative day	15.0 mg.
2nd postoperative day	10.0 mg.
3rd postoperative day	6.0 mg.
4th postoperative day	4.0 mg.
5th postoperative day	1.83 mg.
6th postoperative day	0.83 mg.

twenty-six additional cases have been added without any deaths. It is definitely known that the absorbability of the drug is proportional to the peritoneal reaction that is present. (7) *Prophylactic Use in Abdominal and pelvic surgery*, in which all cases of chronic salpingitis, hydro-

TABLE V  
CHRONIC PYOSALPINX (15 GM. SULFANILAMIDE POWDER)

1st postoperative day	4.5 mg.
2nd postoperative day	1.55 mg.
3rd postoperative day	0.61 mg.
4th postoperative day	0.06 mg.

cannot be aligned and held properly in place, the placing of vitallium metal screws and plates into the bone to hold the fractures in situ. Sulfanilamide powder, 20 Gm. for adults and proportionally smaller amount for children, is placed into the fracture site both beneath and on top of the periosteum and the subcutaneous area. The wound is closed without drainage and a plaster of Paris splint applied to immobilize the part. It is interesting to note here that we have had some mental worry in some of these cases of compound fractures due to a temperature rise on the third and fourth days which would progressively go higher each day. All of these patients were receiving sulfanilamide by mouth and on discontinuance the temperature subsided to normal. (3) *Carbuncles*, the treatment of which has been satisfactory in our hands by the use of intravenous anesthesia, thorough incision with the radioknife, removal

TABLE I

ABSORPTION FROM DENUDED AREA FOLLOWING RADICAL RESECTION OF BREAST  
(30 GM. SULFANILAMIDE POWDER)

1st postoperative day	6.3 mg.*
2nd postoperative day	7.8 mg.
3rd postoperative day	9.7 mg.
4th postoperative day	3.1 mg.
5th postoperative day	0.88 mg.
6th postoperative day	0.06 mg.
7th postoperative day	None available

\*In Tables I-V, rate as shown is in milligrams per 100 c.c. of blood serum.

of the infected tissue by electrocoagulation, and packing with sulfanilamide powder. Freedom from pain and sepsis following this procedure has been the rule. (4) *Local abscesses*, treatment of which with incision and drainage and daily applications of sulfanilamide powder dusted into the cavity has shortened the duration of the infection and apparently aided materially in the cure. We have noted breast cases referred to us for radical resection in which biopsies had been made in other small hospitals in which there was infection from previous surgery with marked induration around the carcinomatous breast from incision and not from the malignancy. These cases have been handled satisfactorily by the use of 20 Gm. of sulfanilamide powder; in one case as much as 30 Gm. were dusted into the wound before closure of the skin flap. These cases

TABLE II

ABSORPTION FROM NORMAL PERITONEUM WITH NO PERITONITIS  
(15 GM. SULFANILAMIDE POWDER)

1st postoperative day	12.5 mg.
2nd postoperative day	9.7 mg.
3rd postoperative day	7.8 mg.
4th postoperative day	3.1 mg.
5th postoperative day	0.88 mg.
6th postoperative day	0.5 mg.
7th postoperative day	None; all pus and symptoms of pyelitis clearing up

have progressed satisfactorily without infection and the large raw area has offered great absorbent powers as will be shown in Tables I-V on the rate of absorption. One patient with frank acute appendicitis with bilateral pyelitis complicating the disease had 20 Gm. of sulfanilamide powder placed in the peritoneal cavity which cured her pyelitis without further administration of the drug. (5) *Appendical and pelvic abscesses*, which have been treated most successfully without drainage by incising and irrigating the abscessed cavity, placing 20 to 30 Gm. of sulfanilamide powder into the abscess, and closing the abdomen without drain-

TABLE III  
APPENDICAL ABSCESS (15 GM. SULFANILAMIDE POWDER)

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2nd postoperative day	1.4 mg.
3rd postoperative day	0.51 mg.
4th postoperative day	0.41 mg.
5th postoperative day	0.09 mg.
6th postoperative day	0.03 mg.
7th postoperative day	Negative; patient discharged from the hospital

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TABLE IV  
GENERAL PERITONITIS (15 GM. SULFANILAMIDE POWDER)

1st postoperative day	15.0 mg.
2nd postoperative day	10.0 mg.
3rd postoperative day	6.0 mg.
4th postoperative day	4.0 mg.
5th postoperative day	1.88 mg.
6th postoperative day	0.88 mg.

twenty-six additional cases have been added without any deaths. It is definitely known that the absorbability of the drug is proportional to the peritoneal reaction that is present. (7) *Prophylactic Use in Abdominal and pelvic surgery*, in which all cases of chronic salpingitis, hydro-

TABLE V  
CHRONIC PYOSALPINX (15 GM. SULFANILAMIDE POWDER)

1st postoperative day	4.5 mg.
2nd postoperative day	1.55 mg.
3rd postoperative day	0.61 mg.
4th postoperative day	0.06 mg.

salpinx, supravaginal hysterectomy, and tubo-ovarian abscess with removal are treated by the use of sulfanilamide powder dusted into the area of the pelvis. The stump of the cervix particularly has been closed with no complications in any cases after its use. Its use is advantageous as a prophylactic measure following any gastrointestinal surgery with soiling of the peritoneum.

#### RATES OF ABSORPTION

The typical rate of absorption is shown in Tables I-V.

The maximum concentration in any of our cases has been 19.5 per cent. The minimum concentration shown has been 1.9 per cent. The effectiveness of the drug is lost if and when concentration falls below 1 mg. per cent. In our opinion the ideal concentration desired is from 6 to 10 mg. per cent.

#### CONCLUSION

1. Attention is called to the use of sulfanilamide powder locally.
2. The various methods and types of cases aided by it are herein noted.
3. Sufficient concentration in the serum can be obtained in conditions requiring its use.
4. Autoclaving destroys the effectiveness of the drug.
5. Its rate of absorption is dependent upon the vascularity of the area in which it is placed.
6. Attention is directed to its use in war surgery as a prophylactic measure in the field.
7. No complications can be noted in any cases under our care due to the drug.

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# SURGERY OF BRAIN TUMORS TODAY AND TEN YEARS AGO\*

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TEN years ago I based a paper upon a series of 298 brain tumors which I had removed in the course of twenty years. In the first ten years there were 38; in the second ten years, 260. In the past ten years, the third decade of my work, we have removed 796 brain tumors. We have, therefore, a series of 1,094 brain tumors, removed partially or *in toto*, on which these remarks are based. This material can be studied from many angles. Naturally, in an address such as this, only a few points can be stressed.

In my paper ten years ago I discussed methods of diagnosis and technical methods of tumor removal. Since then, these technical methods have been pretty well standardized and no new methods have been introduced, although we have learned to use more effectively the methods we then had at our disposal, some of which were new at that time. On the diagnostic side there is a constant improvement, though nothing very fundamental has been added. A good deal is being written nowadays about electroencephalography and its relation to diagnosis. About these things I shall have a few words to say later, but for the most part I shall devote my remarks to a different phase of the subject.

For the general practitioner, as well as for the specialist, one point is always of deep interest; namely, the operability of tumors and their malignancy. On this point our series gives valuable information. I have classified the tumors according to the types that we recognize today (Table I).

TABLE I  
PATHOLOGIC CLASSIFICATION OF 1,094 BRAIN TUMOR CASES

Meningiomas	178	16.4%
Astrocytomas	124	11.3%
Acoustic neuromas	90	8.2%
Pituitary tumors	70	6.4%
Hemangioblastomas and angiomas	50	4.5%
Cranio-pharyngiomas (suprasellar cysts)	25	2.2%
Medulloblastomas	67	6.1%
Ependymomas	48	4.3%
Oligodendrogliomas	26	2.3%
Miscellaneous tumors (under 1 per cent)	138	12.6%
Spongioblastomas multiforme and unclassified	207	18.9%
Malignancies, metastatic	71	6.4%

In this table, I have placed those brain tumors most commonly encountered and have placed them in order of their malignancy, beginning with the benign and working down to the most malignant. From this,

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you will see that about 45 per cent of all brain tumors fall into the benign group and that another 6 per cent are semibenign; that is, they are very slow growing and either can be totally removed, or these patients, by repeated operations over a period of years, can be kept comfortable and often are able to follow their occupation even though it be a very strenuous one. Some years ago a patient who was a cowpuncher used to come to me every twelve or eighteen months to have some more tumor removed so that he could carry on (Fig. 1). In this way it was possible to keep him comfortable and working for a number of years.



Fig. 1.—X-ray plate of a case of ependymoma. The peculiar fluffy appearance of the calcification is characteristic of this type of tumor.

*Meningiomas.*—The most favorable type of tumor is the meningioma. It is only in rare instances that these undergo malignant degeneration. They are well encapsulated and can be removed completely. It may be possible to remove them in one mass, but, as they frequently are very large, it is wiser to remove them piecemeal. This is safer though not so spectacular. (Fig. 2.) The sudden removal of a huge tumor—they often weigh several hundred grams—may throw the patient into shock,

while this danger may be completely avoided when it is removed in pieces. Removing a tumor in this fashion necessitates more exacting methods of hemostasis, and this is where electrocoagulation has become indispensable. The removal of these tumors is tedious and time-consuming. Frequently the brain tissue has to be pushed back and great gentleness is necessary in order not to interfere with the function of this brain tissue. Of course, the importance of sparing the surrounding brain tissue depends greatly upon the location of the tumor. Thus, if a tumor is on the left side, near the origin of the sylvian fissure, injury to the speech mechanism is an ever-present danger. It is impossible to be certain during an operation whether the speech center has been permanently injured. For this reason, such operations, in which there is a question

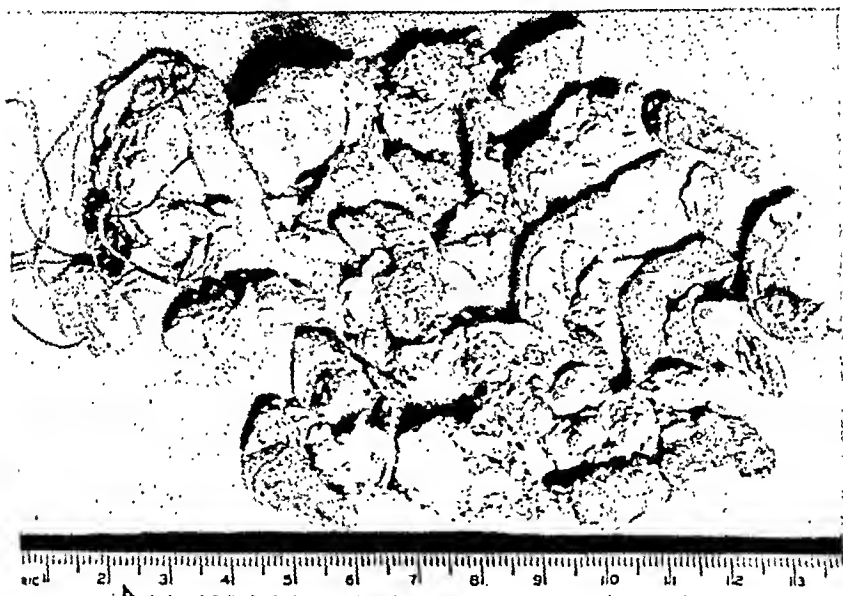


Fig. 2.—Olfactory groove meningioma that was removed piecemeal.

of saving the speech mechanism, are better carried out under local anesthesia. The anesthetist, in talking to the patient, can keep the surgeon informed of any speech disturbance. This information is a great comfort and is of great prognostic value. If, after the tumor has been removed, the patient speaks even an occasional word, the surgeon may be certain that the patient's speech mechanism is intact. At the time the operation is completed, the patient may not be able to speak, due to the edema of the brain which lay adjacent to the tumor, but, thanks to the brief period of speech after the tumor was removed, one is able to assure the family and the patient that speech will return. This is most comforting to both the surgeon and the family. I recently went through such an experience. A woman, 65 years of age, had a meningioma just below her sylvian artery (Fig. 3). Before operation her speech had

been perfect. At the end of the operation she said a few words, and then for over a month she said nothing but "no." Usually speech begins to improve in a week or two and longer delay in recovery is harrowing to both the surgeon and the family. Often it worries the patient greatly and the worry, at least in this case, increased the inhibition which had to be overcome before she started to speak. It was, therefore, very comforting to be able to reassure the relatives that there would be ultimate recovery.

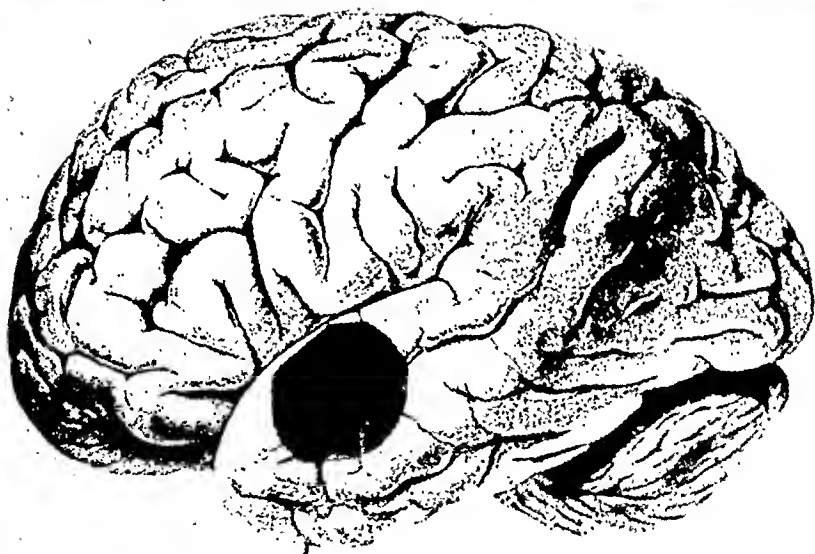
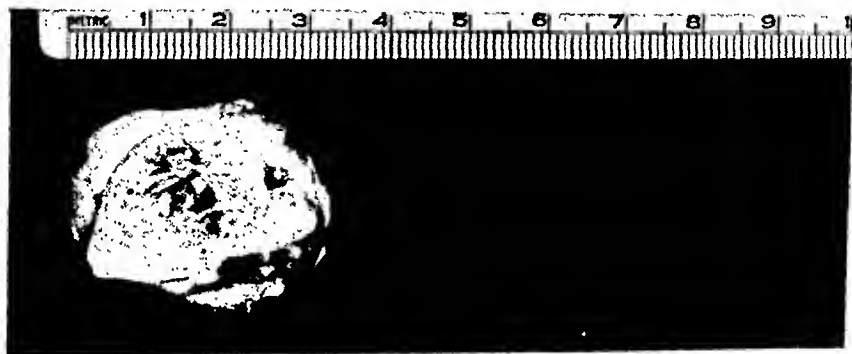


Fig. 3.—Meningioma and its location causing marked speech disturbance from which patient recovered completely.

Cases in which speech may be affected are, however, the only ones that I do under local anesthesia today; all others are done under avertin with the addition of local anesthesia. Ten years ago we still were doing everything under local anesthesia.

In removing any tumor, blood vessels have to be occluded. I had the impression ten years ago that electrocoagulation, which then was a new

procedure for occluding vessels, was preferable to the old silver clips. Our experience since then has confirmed this, and for all vessels that have to be occluded—"tied"—electrocoagulation is used if possible. Occasionally silver clips may be necessary.

The mortality in the removal of meningiomas has steadily gone down. In the 117 cases operated upon in the last ten years, it was 19 per cent; while in the last five years, in 61 cases, it was only 9.8 per cent.

*Astrocytomas.*—The second most frequent tumors in the benign group are the astrocytomas. Many of these, especially when they occur in the cerebellum, are cystic in character. The results of operation upon these cases are eminently satisfactory. If the cyst is evacuated, all pressure signs recede, but this will not effect a cure. To cure these cases the solid portion, the growing portion spoken of as a nubbin, must be removed; otherwise, sooner or later there will be a recurrence. The cystic fluid in these tumors is secreted either by the solid portion of the tumor or is the result of degeneration; but why some of these tumors, which histologically are indistinguishable from one another, should produce a large amount of fluid and others not, is not at all clear. This is one of a number of instances which suggests that there may be a chemical interaction between tumor cells and normal brain tissue and that different regions of the brain react differently to the same group of cells.

We also lack, thus far, any adequate explanation of the fact that some tumors develop much more frequently in certain regions of the brain than in others.

*Acoustic Neuromas.*—The third large group consists of the acoustic neuromas, tumors which grow from the eighth nerve itself. In our series there were 89 cases, which places these as the third most common tumor in the benign group. In the last ten years there has been a greater change in the handling of this type than in the treatment of any other type of brain tumor. The first important contribution about them was made twenty years ago by Cushing in his book on *Acoustic Neuromas*. He advocated at that time, in fact believed up to his death, that the best treatment was a partial or, as he termed it, intracapsular removal of these tumors. The operation consisted of a bilateral cerebellar exposure with retraction of the cerebellar lobe on the side of the lesion. The capsule was split and as much of the tumor was removed as the surgeon deemed wise, but most of the capsule was left and sooner or later these patients had a recurrence. Sometimes they were free of symptoms for many years. I have some patients operated upon by that method who have been free of symptoms for many years, one of them for as many as eleven years. Today the operative approach is unilateral and, in order to get enough room, after reducing pressure by a ventricle puncture, part of the lateral lobe of the cerebellum is resected (Figs. 4 and 5). If one is careful not to injure the nuclei of the cerebellum, the resection of the cerebellum does not give rise to any serious symptoms, at most perhaps a transient ataxia. In fact, resecting the cerebellum is less harm-

ful than retracting it for a prolonged time because prolonged retraction injures its blood supply, thus destroying its function; furthermore, leaving traumatized avascular tissue in the wound increases the possibility of an infection. This operation is extremely difficult; in fact, I consider operations for eighth nerve tumors among the most difficult we have to perform. There is no operation in which a skillful assistant is so important. The results, however, are better than by the older method and,

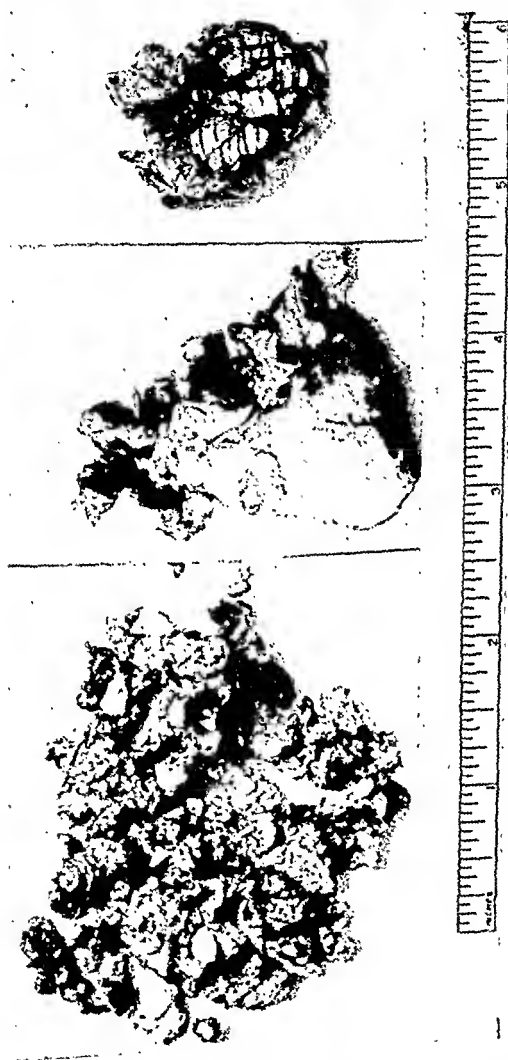


Fig. 4.—Acoustic neuroma and cerebellum that was resected.

though our mortality is still much too high, in the last 20 cases it has been 20 per cent, while prior to that time it was much higher. I feel certain that in the next five years our figures will be much better. One reason for this high mortality is that 4 of the 7 deaths have been from operations on recurrent tumors and the universal experience has been that the mortality on recurrent eighth nerve tumors is vastly higher than when the initial operation has been a radical one.

There are certain points in the operation and postoperative treatment of these tumors which, if overlooked, spell disaster. These tumors lie, as a rule, in contact with the vagus and glossopharyngeal nerves and are usually imbedded in the side of the pons. Sparing these nerves is all important. The dissection must be carried out slowly and with meticulous attention to hemostasis. This is one of the few cranial operations in which electrosurgery cannot be used freely. The heat from the electro-

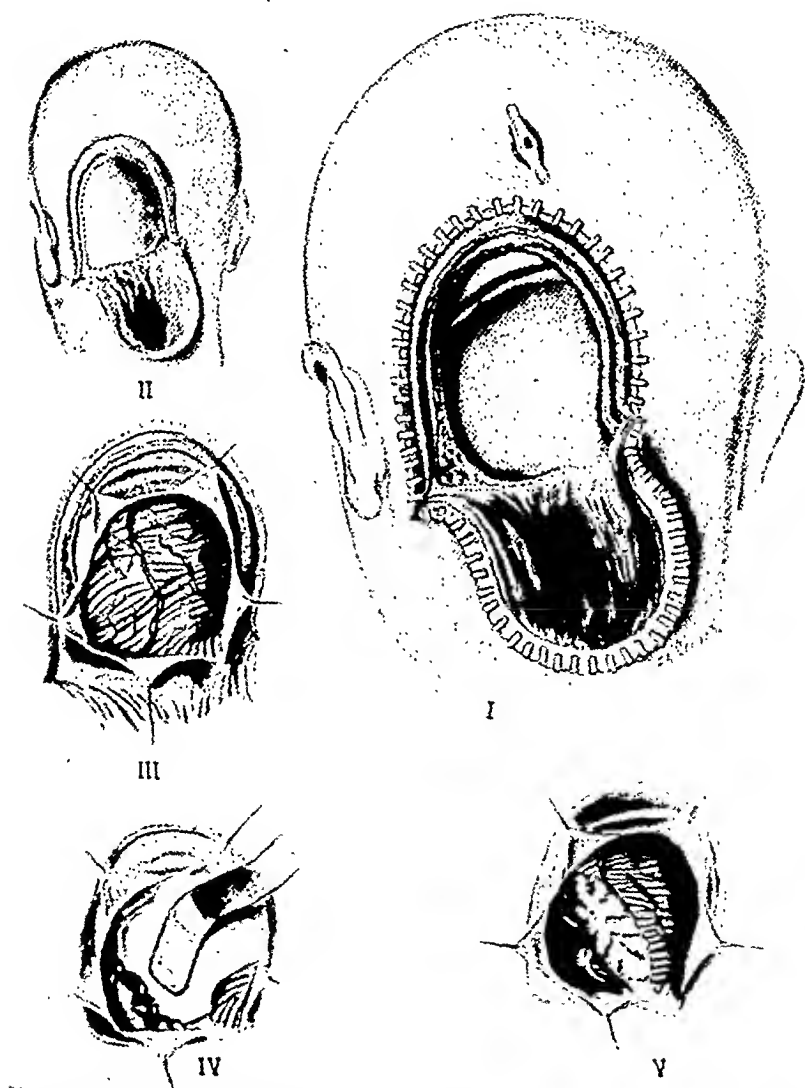


Fig. 5.—Steps of unilateral exposure of acoustic neuroma. (From Sachs: *Surgery of the Acoustic Nerve*, Nelson's Loose Leaf Surgery of the Ear, Charles C Thomas, Publisher.)

surgical unit may injure the pons or the vagus nerve. Such injury may interfere temporarily or permanently with the patient's swallowing or speaking. This must be kept in mind in the postoperative care. I have lost several patients, in years gone by, because I have permitted these patients to be given food or water too soon; as a result they developed pneumonia. The routine today is absolutely nothing by mouth for a day or two and then only feeding through a small nasal tube until we are certain the patient swallows normally.

*Medulloblastomas, Oligodendrogliomas, and Ependymomas.*—We now must consider the tumors that are less favorable; many of these are not encapsulated and show some tendency to malignancy. They fall into three groups: medulloblastomas, oligodendrogliomas, and ependymomas. The first of these, medulloblastomas, occur most frequently in children, and usually in the posterior fossa. It is the one brain tumor that is markedly radiosensitive. This fact has given rise to a rather lively controversy regarding its treatment. One group of surgeons believes that medulloblastomas should be treated with deep therapy and not be operated upon at all. A second group believes in doing merely a biopsy and then giving therapy, while a third group believes in doing a radical excision and following it up with x-ray. I cannot discuss today the various arguments held by the proponents of these different theories but shall say merely this, that I personally do not believe in treating any case with x-ray unless the histology of the tumor is known. Radical removal followed by deep therapy, if the tumor is the radiosensitive type, seems to me to hold out the best chance for the patient. Up to the present time, treatment of deep-seated lesions by x-ray or radium therapy only, has not in our experience accomplished either what radical removal has accomplished or, still better, radical removal plus therapy. Using therapy without knowing the pathology of a tumor has the further serious objection that a mistake in diagnosis may readily occur and that a tumor, which is not at all radiosensitive yet perfectly operable, may be treated by x-ray instead of being removed by operation. Such treatment involves a loss of precious time. It is impossible either from clinical symptoms or from x-ray findings to know whether or not a tumor belongs to the radiosensitive variety. One can do no more than suspect this. Furthermore, employing the therapeutic test is hazardous, for there may be a temporary recession of symptoms which gives one a false sense of security. This past year we have had exactly this experience. A child with a posterior fossa lesion had been treated with x-ray. For a few weeks there was some improvement so that x-ray treatment was repeated in spite of a steady advance of symptoms. When the child was brought to us, its condition was such that we had to operate promptly, and we found and removed a cholesteatoma. This rare type of tumor—we have had only eight in our entire series—is not affected by x-ray therapy at all, but is quite readily removed.

The two other types which I am considering in this group, oligodendrogliomas and ependymomas, are not radiosensitive. They grow slowly but are more likely to recur after operation because they are not encapsulated and their margins, therefore, not so well demarcated. These tumors can sometimes be completely removed. It is always an advantage to the surgeon if he knows, or may suspect before he undertakes an



Fig. 6.—Papilloma of the fourth ventricle.

operation, the nature of the tumor. This is frequently possible with these tumors because of the peculiar type of shadow they cast in the x-ray plate (Fig. 1). Given this clue, the cautious surgeon plans his operation somewhat differently, for these tumors frequently extend well beyond the areas of calcification; consequently one must provide ample room for their removal by making larger bone flaps.

There are a good many other tumors which I have grouped under the heading miscellaneous. No one type amounted to more than 1 per cent. The prognosis for some of these is very favorable, such as papillomas of the choroid plexus, which usually are located in the fourth ventricle (Figs. 6 and 7), or cholesteatomas. Others in this group are malignant and have a poor prognosis. None of them warrants special discussion here since they do not present any different diagnostic or surgical problems.



Fig. 7.—Papilloma of the fourth ventricle.

*Pituitary Tumors.*—The pituitary tumors, however, present problems which are entirely different from those of any other intracranial tumors. Practically the only symptom that brings patients suffering from a pituitary lesion to operation is loss of vision. This loss of vision is different from that caused by a brain tumor; it is characterized by a peculiar field defect, bitemporal blindness, and by the absence of choked disc.

This visual disturbance is produced in a different way; it is due to direct pressure on the optic chiasm. Because of the peculiar arrangement of the fibers in the chiasm, when the pressure is exerted equally on the two sides, typical bitemporal blindness occurs. In the rare cases in which the pressure is not symmetrically exerted, the field defect may be of a different type.

The operative treatment has been well standardized. Whereas there was a time when cases of pituitary disease with an enlarged sella turcica were operated upon through the nose, transphenoidally, today all neurological surgeons do these operations by an intracranial route. In fact, the only one who still employs the intranasal approach is Hirsch, formerly of Vienna, now in Boston.

The advantages of the intracranial procedure are: (1) a sterile field which, even under the most favorable circumstances, the nose cannot be; and (2) a larger field which permits adequate exposure of the tumor and enables the surgeon to undertake a more radical procedure. The one disadvantage is the risk of hemorrhage into the tumor bed after operation. This, however, requires meticulous hemostasis and very careful post-operative observation so that, if a hemorrhage occurs, the clot may be promptly evacuated. My own custom, in case of doubt, is to drain the sella for twenty-four hours to avoid this complication.

In the course of years I have found that some of these patients have recurrences; this can be obviated best by postoperative deep therapy. I do not believe in treating a pituitary tumor case, in which there is marked loss of vision, with deep therapy first, and operating only as a last resort. The danger of losing vision permanently while trying x-ray therapy—for weeks or months may elapse before one can know whether x-ray helps—is a risk I am unwilling to take.

*Spongioblastoma Multiforme.*—Lastly, we must consider the malignant type of glioma, the spongioblastoma multiforme. Here is a field in which much still has to be done, for, up to the present time, very few patients with this type of tumor have been permanently cured. These tumors are infiltrating and rapidly growing and, as a rule, patients with this type of tumor die within two years after the onset of symptoms. How best to deal with these cases has given rise to considerable discussion. It is usually impossible to make the pathologic diagnosis before operation. One may suspect this type when the patient's symptoms develop rapidly, but this is uncertain and practically all cases with brain tumor must be operated upon. Many of these can be diagnosed grossly at the operating table. The difference of opinion that arises is how to deal with the case if one finds a malignant glioma. One group of surgeons advocates doing nothing but a biopsy and closing up; a second group advocates taking out as much of the tumor as possible and sewing up the dura tightly; the third group, in addition to removing as much of the tumor as possible, leaves a large decompression to relieve the pa-

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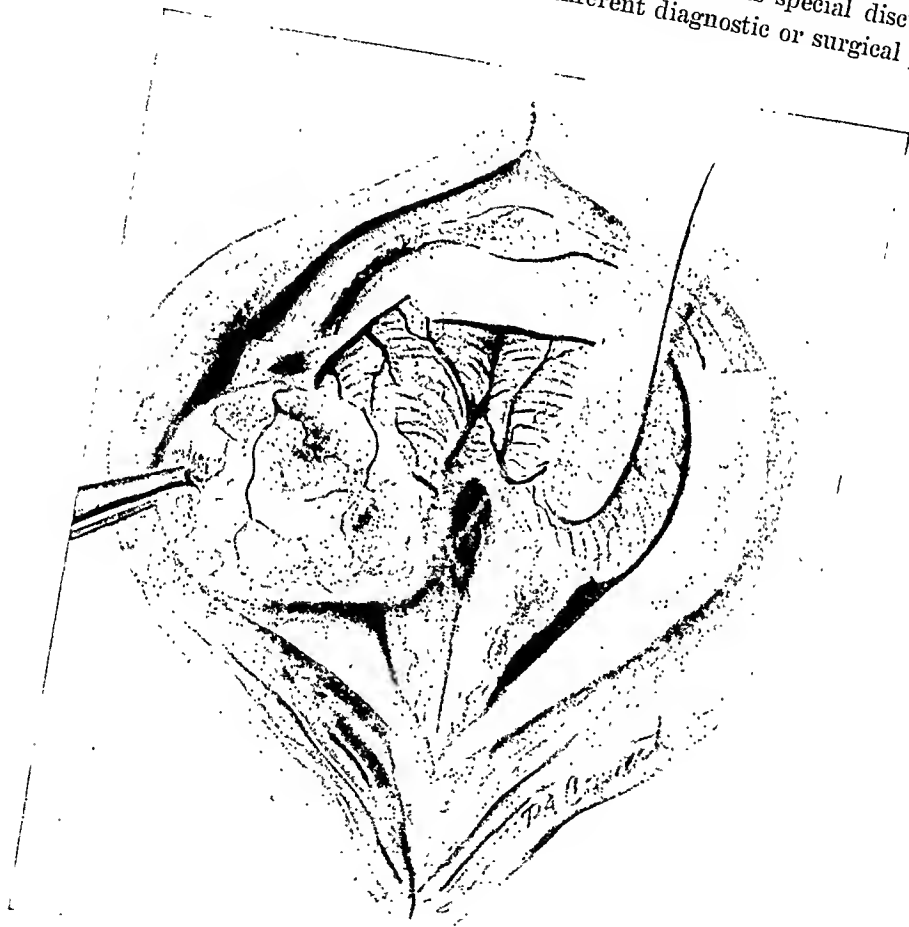


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tient's pressure symptoms if and when the tumor recurs. Experience has shown that the first method, not to attempt to remove the tumor, gives no relief whatever and is attended by an immediate, very high postoperative mortality. On the other hand, removing the tumor usually gives the patient complete relief from his headache and saves his eyesight, while the focal symptoms, such as paresis and aphasia, may clear up. Then, if the dura has been closed, when the tumor recurs the patient dies quickly. This second group does not believe, ever, in operation a second time upon a patient with this type of tumor.

I belong to the third group. I do a decompression after a radical removal with the idea of giving the patient relief as long as possible. If there is no decompression, the patient who gets a recurrence suffers as much as he did before his first operation, while in this way he may be quite comfortable, often to the very end. I do believe, in some cases, in operating repeatedly, two and three times even, if by so doing the patient can be kept comfortable and does not have too much disability. Of course, the family must understand that this is only a palliative procedure and will not effect a cure.

I can see no justification for the attitude of the first group since their procedure not only hastens the end but often precipitates it. I can see the point of view of the second group; however, in my experience, the majority of families want their relatives' lives prolonged if possible, and I for one am not willing to recommend euthanasia. My point of view is excellently expressed in that fascinating book, *As I Remember Him*, recently published by Hans Zinsser, late Professor of Bacteriology at Harvard, when he says: "I have always come to the conclusion that the safest principle, except in a few special instances, such as the last stages of cancer, leukaemia or of Hodgkin's disease, is to continue to work with all means at one's disposal as long as the pulse keeps going and the breathing continues."

In the past ten years our percentage of tumor removals, partial or complete, has greatly increased and, in the past five years, it has amounted to from 95 to 97 per cent of all tumors operated upon, and, though we are more radical than we used to be, our mortality is going down. We are removing tumors now that we didn't venture to tackle ten years ago, notably tumors in the ventricles. This has been made possible by the extensive use of electrosurgery. Any incision into the brain used to be a formidable procedure, but that time has passed. Today we have no hesitation in incising it and even excising large blocks of tissue. A great aid also in these procedures, especially if we are dealing with an infiltrating glioma, is a suction apparatus.

Eight years ago we changed our method of anesthesia and now use practically nothing but avertin with the addition of local anesthesia. We have given avertin in over 2,000 cases and find it more satisfactory and safer than any other anesthetic we have ever used. It requires a

skilled anesthetist to administer it, and there are little tricks upon which its successful use depends. This method of anesthesia has contributed greatly to better results. Not only has avertin been eminently satisfactory, but it has been a great relief to both patient and surgeon. As we use it, the patient knows nothing about his operation and does not even know when he is put to sleep. It is administered in his room, in bed, and the patient is not moved until after he is asleep. Frequently the patient inquires the next day when he is going to be operated upon; whereas, when a patient has been operated upon under local anesthesia, and has required a second operation, he has often dreaded the ordeal and begged for a general anesthetic. Patients who have had avertin do not have this dread.

I have pointed out what a serious problem the malignant gliomas constitute. With the idea of solving this problem, we tried deep therapy directly into the open wound during the course of an operation, but, after trying it for a number of years, we could not convince ourselves that the results were any better than formerly and rarely use it any more.

Though we now know how to relieve patients with infiltrating gliomas, their cure has not yet been solved.

On the diagnostic side we have had no very significant advances, but we have come to make more use than ever of ventriculography. With greatly increased experience our interpretation of air plates has naturally improved. We have found that a large number of views from different angles have helped us to localize difficult lesions more accurately.

We have been trying out electroencephalography and have found that, in a considerable number of cases, it confirms localizations made by other methods. Sometimes it has indicated focal lesions of which there was no evidence by any other diagnostic procedure, and these patients, when operated upon, had no demonstrable lesion. On the other hand, in some cases of meningioma, electroencephalographic examination showed no evidence of a lesion as there is no electrical activity in a tumor itself. For these reasons, therefore, I feel that, though the study of electroencephalographic records is of great interest and may in the next few years yield valuable information, it cannot now replace other recognized methods of diagnosis. In my clinic, at present, we do not feel that we can place great dependence upon it.

Today, just as ten years ago, we rely for our diagnosis primarily on our history, physical examination and ventriculography.

It is just as necessary today as it always has been for men to keep their feet on the ground and learn to evaluate both diagnostic and surgical procedures properly. Anyone—well, almost anyone—can acquire the technical skill to operate, but the most valuable asset for the neurological surgeon always has been and still remains—*judgment*.

## THE MECHANICAL SUPERIORITY OF ANNEALED STAINLESS STEEL WIRE SUTURES AND LIGATURES

DANIEL J. PRESTON, M.D., WILMINGTON, DEL.

THE RELATIVE dependability of surgical suture materials should be part of the fundamental knowledge of every surgeon. If one type of suture material is used routinely for all surgical procedures, the operator may overlook other materials of superior efficiency from lack of familiarity with the various types.

The strength of healing wounds depends upon three main factors: (1) The mechanical resistance of tissues, sutures, and knots to tension; (2) the local tissue reaction caused by suture material, trauma, or infection; and (3) constitutional disease which alters the normal healing process. Dehiscence of abdominal or other wounds is favored by a combination of mechanical factors and biological factors. Mass ligatures, tightly drawn knots, and continuous tight big-bite suturing predispose to local necrosis, infection, and separation of the wound edges. The tension forces in a wound are borne alike by the tissues and by the sutures which hold them together. Strength of sutures and integrity of surgical knots are of obvious importance in maintaining the approximation of wound edges. An important biological factor which favors dehiscence of wounds is the weakening of tissues and delay in healing resulting from the local inflammatory reaction caused by organic suture materials. The sheep protein of catgut produces a marked tissue reaction, the scleroprotein of silk a less pronounced response, and inorganic (wire) sutures the least unfavorable changes.<sup>2</sup>

The favorable clinical results obtained with annealed (18-8) stainless steel wire sutures and ligatures have been in sharp contrast at times with the unfavorable results and failures seen in certain instances where organic sutures (catgut and silk) were used. From laboratory studies and observations on the surgical wards it was found that sutures of stainless steel wire favored the optimum healing of wounds. This prompted the investigation here presented to determine by comparative tests the mechanical efficiency of the several types of suture materials commonly used in surgical practice.

*Method of Testing Tensile Strength of Sutures.*—The tensile strength was determined by the sudden application of a 20 kg. pull on a 5 cm. length of each suture. The apparatus (Fig. 1) consists of a calibrated cylindrical testing scale suspended from the transverse top piece. Two clamps which hold the suture are hung upon the testing scale. A rectangular platform between the lateral uprights bears a 20 kg. weight which is hoisted and joined to the lower clamp. When this platform is suddenly released, pull is exerted upon the segment of suture in the

vertically arranged testing scale and clamp system. A ratchet on the testing scale facilitates an accurate reading as it prevents the calibrated scale from snapping back when the suture breaks. In this way a reading is obtained of the maximum force which the suture segment withstood before breaking.

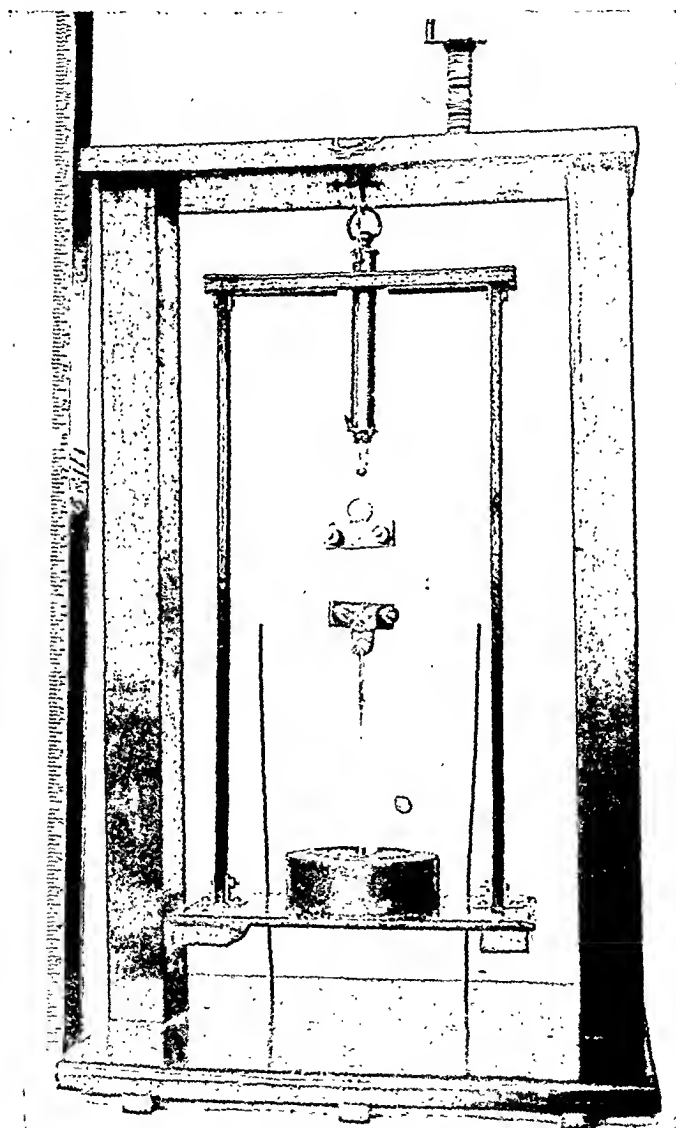


Fig. 1.—Apparatus for testing the tensile strength of sutures and the holding strength of knots.

*Tensile Strength of Sutures.*—In order to compare the tensile strength of any given suture material with another, it is necessary to determine the tensile strength per unit of diameter for each suture to be tested.

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An average of four readings of diameter was made for representative sizes of catgut, silk, and wire. Fig. 4 illustrates these discrepancies in diameter. The greater the variability in diameter of a suture, the less reliable and constant will be its tensile strength. Wire showed the greatest uniformity of diameter.

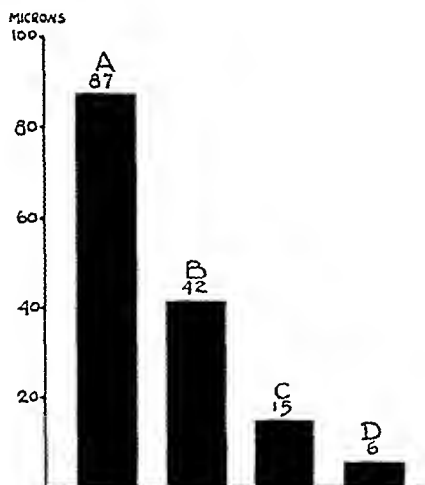


Fig. 4.—The average variability in the diameter of sutures expressed in microns. A, chromic catgut; B, plain catgut; C, black braided serum-proof silk; D, annealed stainless steel wire.

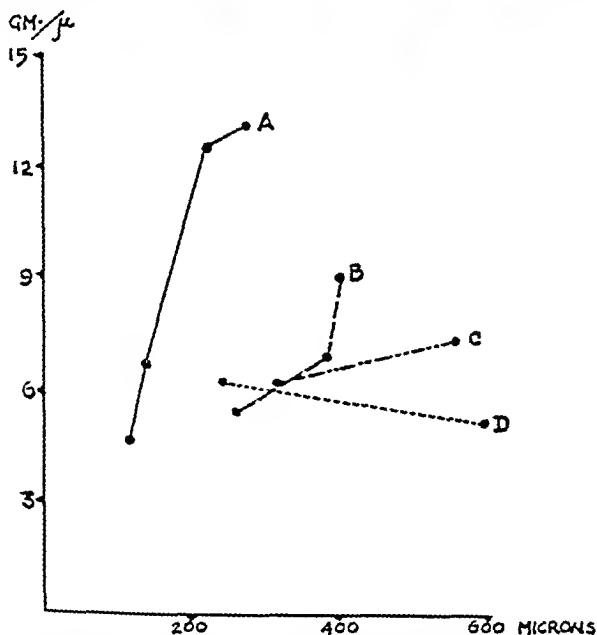


Fig. 5.—The tensile strength of sutures in grams per micron of diameter is plotted against the diameter in microns to show the relative change in tensile strength as the diameter is varied. A, annealed stainless steel wire; B, black braided serum-proof silk; C, chromic catgut; D, plain catgut.

By dividing the tensile strength (grams of pull registered on apparatus) by the diameter of the suture expressed in microns, one can justifiably compare the tensile strength of, say, No. 3 chromic catgut with No. 1 silk by expressing their tensile strengths as grams per micron.

Both large and small sizes of the following materials were used for these tests: plain catgut, chromic catgut, two brands of serum-proof black silk, and annealed 18-8 stainless steel wire. The average of four tests for each size of each material was recorded.

Chromic catgut was appreciably stronger than plain catgut. Silk was only slightly stronger than chromic catgut. Wire was considerably superior in strength to catgut or silk (Fig. 2).

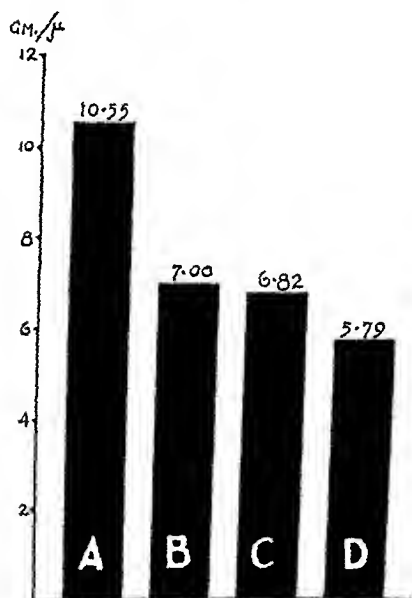


Fig. 2.

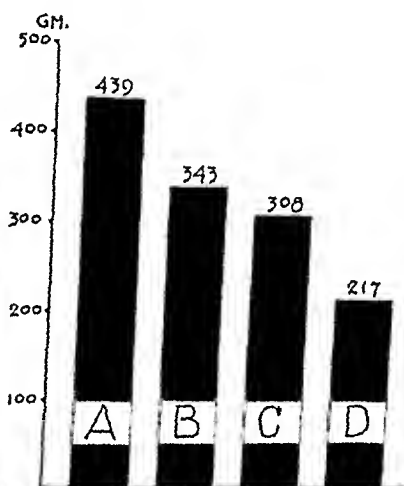


Fig. 3.

Fig. 2.—The average tensile strength of sutures in grams per micron of diameter. A, annealed stainless steel wire; B, black braided serum-proof silk; C, chromic catgut; D, plain catgut.

Fig. 3.—The average variability in tensile strength of sutures expressed in grams. A, two brands of black braided serum-proof silk; B, chromic catgut; C, plain catgut; D, annealed stainless steel wire.

*Variability in Tensile Strength of Sutures.*—By analysis of the tensile strength tests it was found that wire gave the most constant values for all sizes. Silk proved to be the least reliable. Fig. 3 is a graphic comparison of the average variability in the tensile strength of silk, chromic and plain catgut, and annealed stainless steel wire. The greater the variability in tensile strength, the less reliable a suture becomes.

*Variability in Diameter of Sutures.*—Manufacturers do not follow a standard method of grading the size of sutures so that two brands having the same commercial size on the label may vary considerably in the measured diameter of the sutures. Since the diameter is an important determining factor in the tensile strength, the size indicated on the label may be misleading concerning the tensile strength of a suture.

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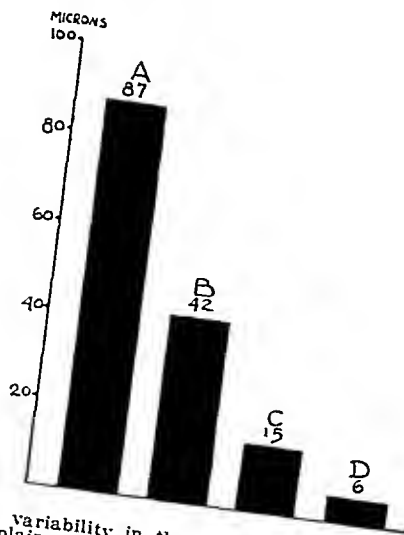


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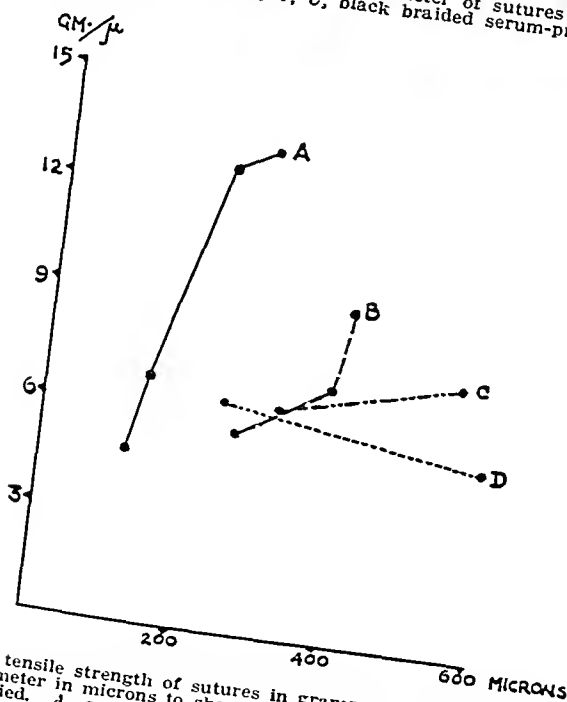


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*Relation of Suture Diameter to Tensile Strength.*—In Fig. 5 the tensile strength in grams per micron is plotted against the diameter in microns for various sizes of the four different kinds of suture materials and shows the relative change in tensile strength as effected by varying the diameter. Plain catgut was the only material tested which showed a decrease in tensile strength per unit of diameter as the size of the suture was increased. Stainless steel wire showed a marked increase in tensile strength with relatively little increase in the diameter. The heaviest wire tested was approximately the same diameter as the finest silk and catgut, yet the tensile strength of wire was found to be more than twice that of either silk or catgut.

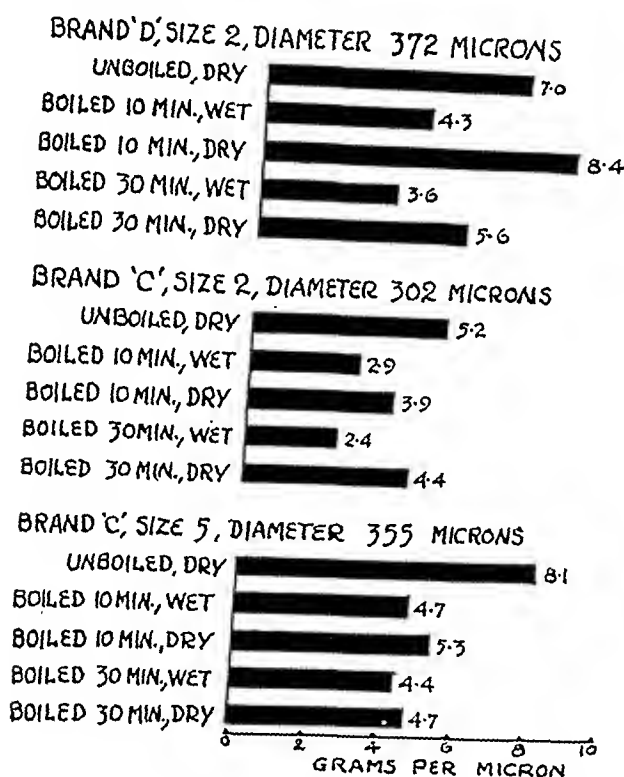


Fig. 6.—The effects of boiling and drying on the tensile strength of braided black serum-proof silk. The tensile strength is expressed in grams per micron of diameter.

*Effect of Boiling on Tensile Strength of Silk Sutures.*—Wet silk which had been boiled ten minutes was found to have lost one-third of its tensile strength. After being boiled thirty minutes, wet silk had lost about one-half of its tensile strength as compared with dry unboiled silk from the same spool. After the wet boiled silk was subjected to air drying for twenty-four hours, an appreciable part of the original tensile strength was regained.

Fig. 6 tabulates the results of tests on boiled silk sutures.

The surgeon should not expect silk boiled for ten minutes to retain more than two-thirds of its original strength. Further weakening is produced by tying a knot which produces sharp angulations in the suture that will not resist as great a pull as a straight strand.

*Method of Testing Surgical Knots.*—The following tests were made to determine what kind of suture material and what type of surgical knot were most secure and gave the greatest holding strength. Each suture was tested with a granny knot, a square or reef knot, a surgeon's knot, and a triple-throw knot (tied as two square knots). All knots were tied in a uniform manner by throwing a loop around a circular support and using a hemostat to grasp one end of the suture as an aid in settling each knot down as firmly as possible without breaking the suture. The components of each knot were made to lie in the same plane and traction with the aid of a hemostat was directed in the plane of the loop. This produced flat knots and avoided insecure twisted knots.

The ends of the suture remaining after the knot was tied were cut off with scissors not farther than 1 mm. from the knot. The loop around the circular support was then divided. The 5 cm. segment of suture bearing the knot was made fast in a clamp at each end and tested for holding strength on the apparatus (Fig. 1) which had been used in determining tensile strength of sutures. Sufficient sudden pulling force was applied in all tests to untie the knot or break the suture.

*Holding Strength of Surgical Knots.*—All plain and chromic catgut knots untied when subjected to the tension test. One-third of the triple-throw knots, made of silk, remained intact, but all of the others (surgeon's, square, and granny knots) untied. All of the stainless steel wire knots, including the granny knots, did not untie in any of the tests.

Catgut and silk knots showed a definite increase in stability of the square and triple-throw knots when the cut ends of the suture were left 5 mm. long. There was no increase in holding strength of granny and surgeon's knots, however, when the cut ends were left 5 mm. long.

Catgut wet with saline solution produced square and triple-throw knots which had twice as much resistance to the pulling force, and, when wet with mineral oil, were five times as resistant. Yet, all these knots untied. Surgeon's and granny knots showed no increase in holding strength when wet with saline solution or mineral oil.

Taylor<sup>3</sup> demonstrated greater friction values for wet catgut as compared with dry catgut. We had expected to overcome some of the frictional forces between the loops of the catgut knots by wetting the suture with mineral oil. The reason why our tests showed an increase in holding strength when this was done is not clear. Oil may make the surface of the suture more porous so that the loops of a knot bite into each other more securely.

Jenkins<sup>1</sup> found that, when the strength of catgut in a wound was dependent upon the knot, the strength lasted only two or three days and failure was due to untying of the knot. The disruption of catgut

knots in wounds is favored by wetting of the suture which causes a swelling with increased elasticity and a tendency for the twisted strands to untwist.

When silk had been wet with mineral oil, the triple-throw knots showed a 70 per cent increase in resistance to the pulling force. The square, surgeon's, and granny knots were essentially unimproved by the oil treatment. Silk could not be wet with saline solution for these tests because of the patented waxy material used by the manufacturers to make the silk serum-proof.

There was no change in the stability of wire knots whether dry, wet with saline solution, or soaked with mineral oil. All wire knots remained tied when tested.

*Reduced Tensile Strength in Knotted Sutures.*—The percentage of decrease in tensile strength of knotted sutures was obtained by comparing the tensile strength of a straight strand of suture with the tensile strength of a knotted suture in which the knot remained intact and the suture broke when tested. The kind of knot employed had no apparent influence on the tensile strength of knotted sutures.

Plain catgut lost 14 per cent; silk, 24 per cent; chromic catgut, 28 per cent; and 18-8 annealed wire, 30 per cent of their original tensile strength when knotted. Tying a knot in the wire causes stretching which apparently weakens the suture and accounts for the marked reduction in tensile strength of knotted wire sutures.

*Disruption of Surgical Knots.*—Knots that disrupted when tested were found to untie by a rolling movement of the second loop which carried it over the short cut end. This rolling movement was a rotation of the suture on its long axis. When the second loop had rolled over the short cut end, the first loop slipped and the knot untied. Therefore it was thought that the resistance of a suture to long axis torsion might be a factor in maintaining the integrity of surgical knots.

A special apparatus was constructed to measure the long axis torsion resistance of sutures (Fig. 7). A 1 cm. length of suture under 1 kg. of tension is fixed in the apparatus between two small circular clutches. By adding analytic balance weights to the aluminum weight pan, the jeweled action central axis combined with the suture rotates through an arc indicated by the pointer on a mounted protractor scale. The weight required to rotate the suture through an arc of 90 degrees was determined for each suture. Stainless steel wire, diameter 120 microns, gave the highest reading of 18.07 Gm. The lowest reading was 0.73 Gm. for No. 10 black silk with a diameter of 421 microns. Catgut, when wet, had about one-half the resistance of dry catgut. Wire sutures were fifteen to eighteen times more resistant to the torsion force per unit of diameter than catgut or silk. No evidence could be found to indicate that long axis torsion resistance is of any aid in maintaining an intact surgical knot.

Friction between the loops of a knot is believed to be the chief factor in preventing surgical knots from untying. Stainless steel wire apparently possessed greater friction between elements of the knots than other materials tested for none of the wire knots untied. When a wire knot is tied, the force required to lay each loop down firmly causes the wire to stretch. By microscopic examination, stretched wire was found to have a roughened surface which accounts for the increased friction and greater stability of wire knots.

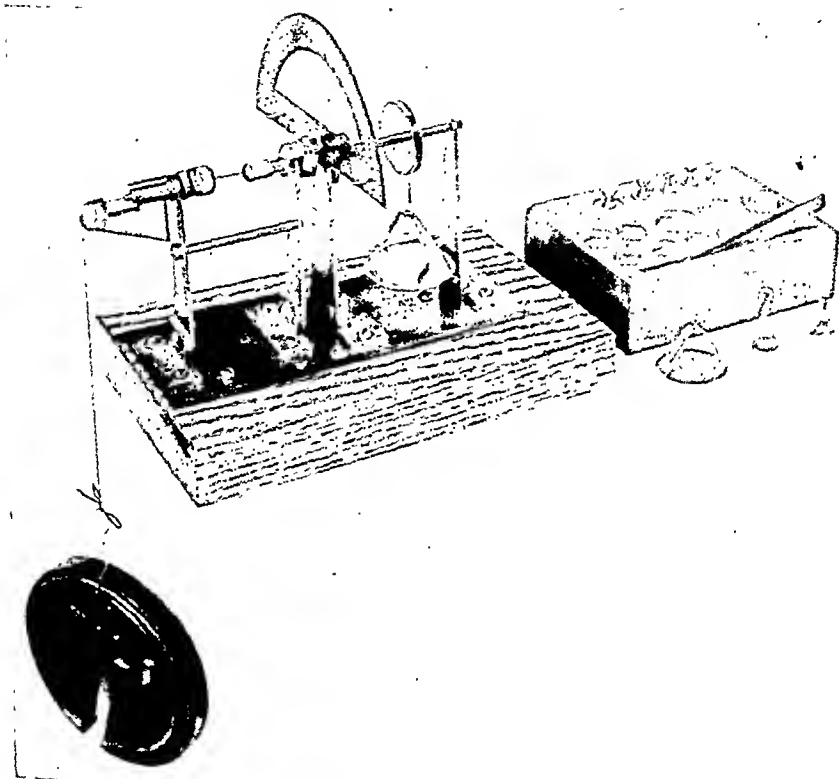


Fig. 7.—Apparatus for determining the long axis torsion resistance of sutures.

#### SUMMARY

Mechanical tests show that catgut has a lower tensile strength per unit of diameter than silk or annealed stainless steel wire. Catgut knots had the least holding strength when compared with silk or wire. The catgut knot most resistant to a pulling force was the triple-throw knot having free ends 5 mm. or more in length.

The tensile strength of silk sutures is greater than catgut but less than stainless steel wire. Boiled wet silk lost one-third to one-half of its original tensile strength. The triple-throw knot was most resistant to the pulling force for silk. The silk surgeon's knot tended to untie even when the free cut ends were left 5 mm. long.

Annealed stainless steel wire sutures are superior to both catgut and silk in tensile strength and holding strength of knots. The mechanical qualities of wire suture are not effected by sterilization or wetting with saline solution or oil.

The holding strength of surgical knots determined by their resistance to a pulling force places the reliability of these knots in the following order: (1) triple-throw knot (tied as two square knots), (2) square or reef knot, (3) surgeon's knot, and (4) granny knot.

When permeable suture materials are wet with saline solution or mineral oil, there is an increase in the holding strength of their knots.

Friction between the loops of a surgical knot is the greatest single factor in maintaining stability and integrity of the knot under tension. Long axis torsion resistance of a suture plays little or no part in preventing knots from untying.

The superiority of annealed stainless steel wire sutures over silk and catgut as shown by laboratory tests have been confirmed by clinical observations. It is hoped that a wider use in surgery will be found for buried wire sutures.

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## THE ROLE OF BRONCHOSCOPY IN THE TREATMENT OF PULMONARY ABSCESS

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THERE is considerable difference of opinion as to the value of bronchoscopy in the diagnosis and treatment of pulmonary abscess. It is not our intention to enter into a discussion of the relative merits of the various procedures which may be employed in the treatment of pulmonary abscess, but rather to present a review of the results that we have obtained over a number of years in the treatment of pulmonary abscess by means of bronchoscopic drainage.

The study to be presented is based on a review of 264 cases of putrid pulmonary abscess seen at the Mayo Clinic over a fourteen-year period, in 193 of which the lesions were treated bronchoscopically. Cases in which the abscess occurred secondarily to tuberculosis, bronchiectasis, and benign or malignant tumor of the bronchus or aspirated foreign body are not included. We have, however, included 6 cases in which there was an antecedent history of a foreign body but in which the foreign body had been aspirated many years preceding the time when the patient came under our observation for pulmonary abscess.

Before attempting to analyze the results that were obtained among the 193 patients treated by bronchoscopic drainage, it would seem advisable to point out briefly the rationale for its use in the treatment of pulmonary abscess. It is of value only in cases in which the abscess communicates with a bronchus. Such a communication is the general rule and is established early during the development of the abscess. When a communication exists, if drainage is adequate, spontaneous resolution of the abscess will generally take place. Lynah and Jackson have pointed out that stenosis of a bronchus communicating with the pulmonary abscess generally occurs, thus interfering with proper drainage and aeration of the abscess cavity. If benefit is to be derived from bronchoscopic aspiration, it is important that the bronchus leading to the abscess be thoroughly dilated. The importance of aeration is especially worthy of emphasis. Brunn, Cutler, and Gross, Allen and Blackman, and others have pointed out that anaerobic organisms are found in approximately 80 per cent of patients with putrid pulmonary abscess, and that undoubtedly much of the benefit that is derived from bronchoscopic drainage is dependent on better aeration of the abscess cavity. In our experience we have been able to establish the most satisfactory dilatation of the stenotic bronchus manually with a heavy pair of dilating forceps. Contrary to Goldman's observation, we have found

that we can often pass an aspirating tube directly into an abscess cavity, and in many instances we have been able to evacuate as much as 500 c.c. or more of thick necrotic material directly from the abscess cavity itself.

The patients in our study are divided into two groups: the first consisted of 140 patients with pulmonary abscess seen between Jan. 1, 1925, and Dec. 31, 1930, inclusive, of whom 105 were treated bronchoscopically; and the second comprised 124 patients seen between Jan. 1, 1931, and Dec. 31, 1938, inclusive, of whom 88 were treated bronchoscopically. The purpose of the division was (1) to determine whether an abscess that had once been classified as responding satisfactorily to bronchoscopic drainage was likely to recur after a ten-year period, and (2) to determine whether or not we had been able to improve on our bronchoscopic technique so far as results were concerned. Approximately the same percentage of patients in the two groups was subjected to bronchoscopy; namely, 75 per cent in the first group and 71 per cent in the second. The results obtained by bronchoscopic drainage have been approximately the same in the two periods and will be discussed later. It is frequently stated that a pulmonary abscess that has been treated successfully by bronchoscopic drainage will often recur after the treatment has been discontinued. In our experience this has not proved true, because only one patient that we classified as having been treated successfully by bronchoscopic drainage in the period between 1925 and 1930 suffered a recurrence during the following ten years; and in this instance the abscess did not recur at the site of the original lesion but was found in the opposite lung many years later.

#### SEX INCIDENCE

As might be anticipated, we found that pulmonary abscess occurred much more frequently in men than in women. In our study there were three times as many men as women.

#### AGE INCIDENCE

No age group is exempt from the ravages of pulmonary abscess. It will be observed in Table I that there was a definite increase in the incidence after the second decade of life and that the maximal numbers of cases in our study occurred during the fifth decade. The youngest patient was 18 months of age, and the oldest 74 years of age. Cutler and Gross expressed the opinion that the prognosis of pulmonary abscess is far better in young adults than in any other age group. This is contrary to our observations, as the best results that we obtained occurred in the fifth decade.

#### ETIOLOGY

No attempt will be made to discuss the mechanism by which pulmonary abscess occurs. Such an attempt would be especially futile inasmuch as the majority of the patients in our study were not ob-

TABLE I

AGE DISTRIBUTION OF PULMONARY ABSCESS IN 193 PATIENTS TREATED BRONCHOSCOPICALLY

AGE IN YEARS	NO. OF PATIENTS
0-10	7
11-20	10
21-30	36
31-40	44
41-50	58
51-60	26
61-70	10
71-80	2
Total	193

served until some time following the development of the abscess. A review of the etiologic factors concerned in the development of pulmonary abscess is summarized in Table II. It is interesting that the cases which followed surgical procedures approximately equaled in number those which did not follow operation. Tonsillectomy was the most frequent etiologic factor in our series of cases. In approximately 90 per cent of the cases in which pulmonary abscess followed tonsillectomy, the operation had been carried out under general anesthesia. This is not surprising for, as Myerson has pointed out, aspirated material can be demonstrated almost invariably in the tracheobronchial tree following tonsillectomy. Kernan expressed the opinion that the post-tonsillectomy abscess responds more satisfactorily to bronchoscopic drainage than any other type. In our experience, however, no marked correlation was noted between the etiologic factor and the response of the abscess to bronchoscopic drainage.

TABLE II

ORIGINATING CAUSE OF PULMONARY ABSCESS IN 264 CASES REVIEWED

FOLLOWING OPERATION		NOT FOLLOWING OPERATION	
PROCEDURE	NO. OF CASES	ETIOLOGIC FACTOR	NO. OF CASES
Tonsillectomy	60	Pneumonia	52
Dental extraction	33	Acute upper respiratory infection	29
General surgical procedures	31	Trauma	3
Post partum	4	Foreign body	6
		Aspiration of secretion	5
		Unknown	41
Total	128 (48%)		136 (52%)

The location of a pulmonary abscess is of the utmost importance in determining whether or not bronchoscopy is advisable. It is obviously unwise and unjust to attempt bronchoscopic drainage if the abscess is located in such a position that it cannot be reached bronchoscopically. Bronchoscopy would be clearly indicated if it were used for no other purpose than diagnosis, for Kramer and Glass have demonstrated that the bronchial distribution to the lobar divisions is constant in approxi-

mately 85 per cent of cases. If one can determine from which bronchus the purulent secretion is exuding, one can localize the abscess in relation to the chest wall in a highly accurate manner. We were able to establish the exact location of the pulmonary abscess in 229 of the 264 cases included in our study, and the classification as to location in the 229 cases is indicated in Table III.

TABLE III  
LOCATION OF ABSCESS AS DETERMINED IN 229 CASES

LOCATION	NO. OF CASES
Right lung, upper lobe	49
Right lung, middle lobe	21
Right lung, lower lobe	64
Left lung, upper lobe	22
Left lung, lower lobe	42
Multiple	31
Total	229

The right lung was the most frequently involved, the lower lobe being the site most frequently selected. Our experience was similar to that of Lukens, that the poorest results as far as bronchoscopic treatment is concerned were obtained in cases in which the abscess involved the lower lobe of the left lung. Contrary to expectation the best results were obtained in those cases in which the abscess involved either the middle lobe of the right lung or the upper lobe of the left lung. A most interesting observation was that slightly better results were obtained in the bronchoscopic treatment of multiple pulmonary abscesses than in that of single pulmonary abscess.

#### RESULTS OF BRONCHOSCOPIC TREATMENT

In order to evaluate properly the benefit to be derived from bronchoscopic treatment of pulmonary abscess, it is necessary to observe the patients over a sufficiently long period of time. One may often obtain a very striking benefit after a single bronchoscopic aspiration and be misled into believing that the patient is well on the way to recovery. Such may be the case for a short period of time, but a recurrence may frequently take place at this stage. Franklin has shown that, in spite of the fact that a pulmonary abscess appears clinically and roentgenoscopically to have cleared up, an abscess cavity can still be demonstrated following instillation of iodized oil. The factor of recurrence has been taken into consideration in the classification as to results obtained from bronchoscopic treatment in our study. The percentage of recurrence is undoubtedly low. As illustrated in the group of 105 cases in which the lesions were treated bronchoscopically before 1931, in only 1 case classified as improved was there a recurrence of the abscess.

The term cured has been reserved for those patients who have no residual pulmonary symptoms, and for those in whom the roentgenographic changes present in the chest, except for a small area of residual

thickened pleura, have returned to normal. The patients classified as improved may have a mild residual pulmonary symptom, such as occasional cough or occasional expectoration, or there may be incomplete disappearance of the roentgenographic findings (Figs. 1, 2 and 3).

The results that we obtained in 193 cases in which the patients were treated bronchoscopically are listed in Table IV. These figures indeed present an encouraging outlook. They are not unusual, as is readily apparent from a review of the literature, but are in close agreement with the results that have been reported previously by Moersch, Clerf, Tucker, Kernan, and other observers. Indeed, they compare most favorably with the results obtained by surgical treatment as reported by Allen and Blackman, Cutler and Gross, Muller, Lambert and Miller, Moore and others.

A review of the results obtained in treatment of pulmonary abscess during the period between Jan. 1, 1925 and Dec. 31, 1930, inclusive, during which 105 patients suffering from putrid pulmonary abscess were treated bronchoscopically, revealed that satisfactory results were obtained in 65.5 per cent of the cases and that the mortality rate was 5.7 per cent. Sixty-one and one-half per cent of the 88 patients treated bronchoscopically during the period between Jan. 1, 1931, and Dec. 31, 1938, inclusive, obtained satisfactory results, and the mortality rate was 3.3 per cent. In other words, very little improvement has taken place during the past decade in our ability to cope with this lesion bronchoscopically.

TABLE IV  
RESULTS OBTAINED FROM BRONCHOSCOPIC TREATMENT IN 193 CASES

RESULTS	NO. OF CASES	
Satisfactory	83}	64%
Cured		
Improved	40}	31%
Unimproved	53}	
Questionable	8}	5%
Dead	9}	
Total	193	

In 5 of the 9 cases in which patients died, as indicated in Table IV, empyema was associated with the abscess, and probably an attempt to treat these patients bronchoscopically should not have been made. In the remaining 4 cases, pneumothorax and pulmonary edema caused the deaths of the patients.

We found that the duration of the pulmonary abscess before treatment was instituted was the most deciding factor in the prognosis. This apparently applies both to surgical and to bronchoscopic management of pulmonary abscess. The duration of the abscesses at the time the patients came under observation is listed in Table V. The shortest period was one week and the longest was ten years. That the duration of the abscess is an important factor in prognosis is well exemplified by



FIG. 1.—Pulmonary abscess of two months' duration following tonsillectomy under general anesthesia. *a*, Before; *b*, after bronchoscopic aspiration.



Fig. 2.—Pulmonary abscess of six months' duration, postpneumonic. *a*, Before; *b*, after bronchoscopic drainage.

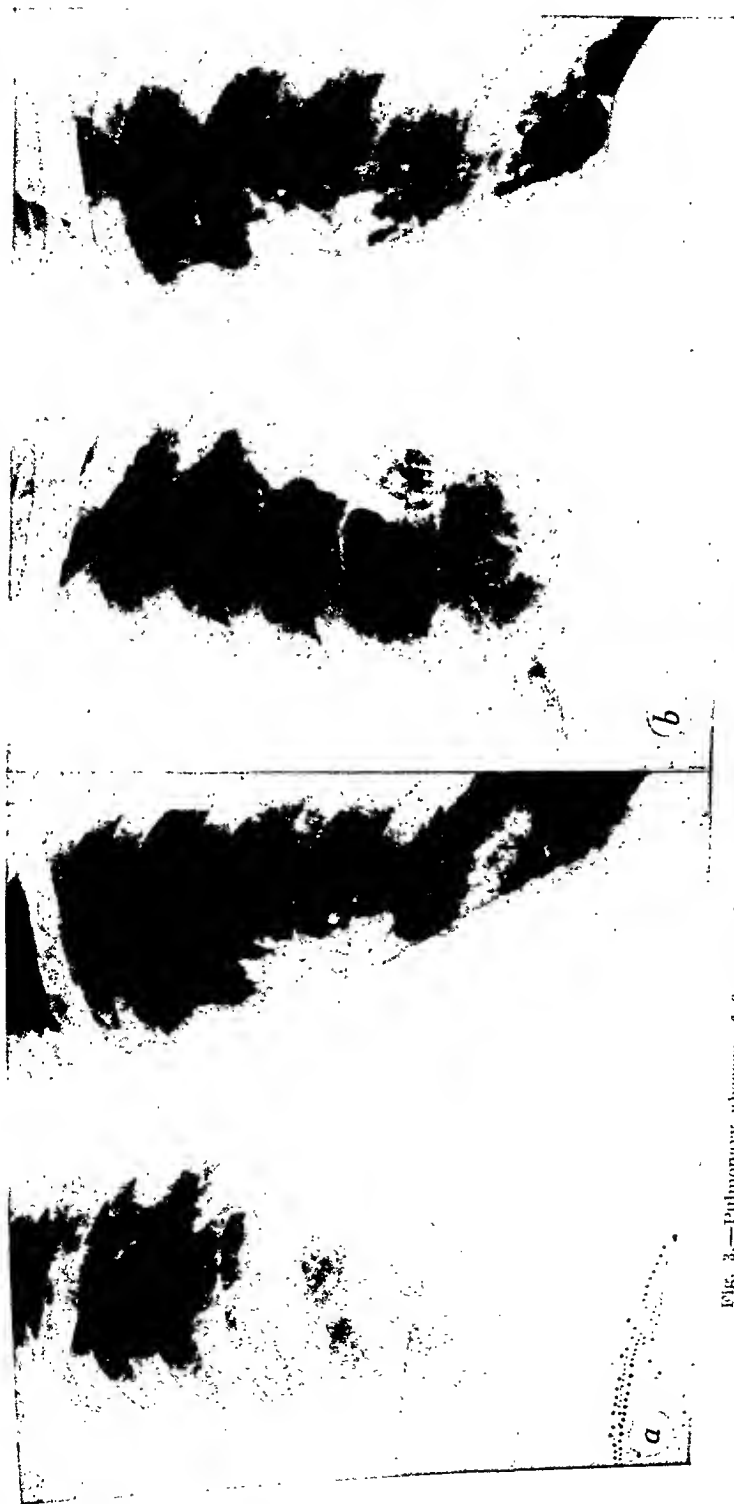


Fig. 3.—Pulmonary abscess of five months' duration, postpneumonia. *a*, Before; *b*, after bronchoscopic drainage.



Fig. 1.—*a*, One month following lobectomy an abscess developed in the opposite lung; *b*, the abscess cleared up under medical management.

## PRIMARY SARCOMA OF THE STOMACH\*

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WE HAVE been stimulated to investigate the subject of sarcoma of the stomach through observing two cases during the last seven years among 135 malignant gastric tumors.

The purpose of this paper is to report these two cases and to review 104 case reports found in the literature of the last ten years, with particular reference to pathology, treatment, and results.

CASE 1.—P. L., male, aged 48 years, was seen Dec. 7, 1932, because of an attack of severe abdominal pain which had begun twenty-four hours before and which was followed by abdominal distention, nausea, vomiting, chills, and fever. At irregular times during the past fifteen years he had had attacks of severe pain, just to the left of the umbilicus, which lasted no longer than a few hours and were relieved by bowel movements. No vomiting accompanied these attacks. Intervals of two years occurred between them. About four weeks before admission pain again appeared to the left of the umbilicus and had continued more or less ever since. It was sharp for short intervals only. It was not aggravated by food taking and was relieved by bowel movements. A mild constipation had been present. No blood had been observed in the stools. During the last few weeks he had worked a little in spite of his continued abdominal discomfort. For three days before admission the abdominal pain had become colicky and more severe. It was in the lower abdomen. Two days before a laxative was taken. A bowel movement occurred with some relief temporarily. Soon, however, the pain recurred in more severe form and was accompanied by nausea and vomiting, which were soon followed by abdominal distention and chills and fever. His condition became acute and he entered the hospital. He appeared to be quite sick. His temperature was 100° F. and his pulse was 120. The entire abdomen was tensely distended, tympanitic, and extremely tender. No rebound tenderness was elicited. No definite mass could be felt. No sounds were heard upon auscultation. Hemoglobin was 55 per cent; erythrocytes, 4,000,000; leucocytes, 15,800; differential count, normal. A plain roentgenogram of the abdomen was normal. The patient was observed for twenty-four hours and then the abdomen was explored through a right rectus incision without a definite preoperative diagnosis. Intestinal obstruction was suspected but not found. A very large immobile, nodular mass was felt in the upper abdomen to which the transverse colon was intimately attached. The intestines were greatly distended. The condition was evidently hopeless and the abdomen was closed. Death occurred on the fifth postoperative day.

*Autopsy.*—In addition to an unaccounted for generalized peritonitis there was found a tumor mass of the stomach. It was both intra- and extraluminal. The intraluminal polypoid portion projected from the posterior wall near the lesser curvature and measured 10 cm. long, 4.5 cm. wide, and 1 cm. thick. It extended from near the cardiac orifice to within 4 cm. of the pylorus. Its mucosal covering was normal except for a craterlike ulcer 2.5 cm. in diameter and 2.5 cm. deep near the cardia. The extragastric portion extended posteriorly and downward be-

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hind the stomach and transverse mesocolon as far as the brim of the pelvis, to the left as far as the hilus of the spleen, and to the right almost to the pylorus. The left half of the transverse colon was firmly attached to its anterior wall. On surfaces made by cutting, the tumor consisted of edematous soft gray tissue mot- tled with recent and old hemorrhages. The liver was studded with metastatic nodules varying from 2 mm. to 2 cm. in diameter. Such deposits were found also in the retroperitoneal and biliary lymph nodes. Microscopic examination showed dense infiltration of the submucosa and muscularis of the stomach by masses of

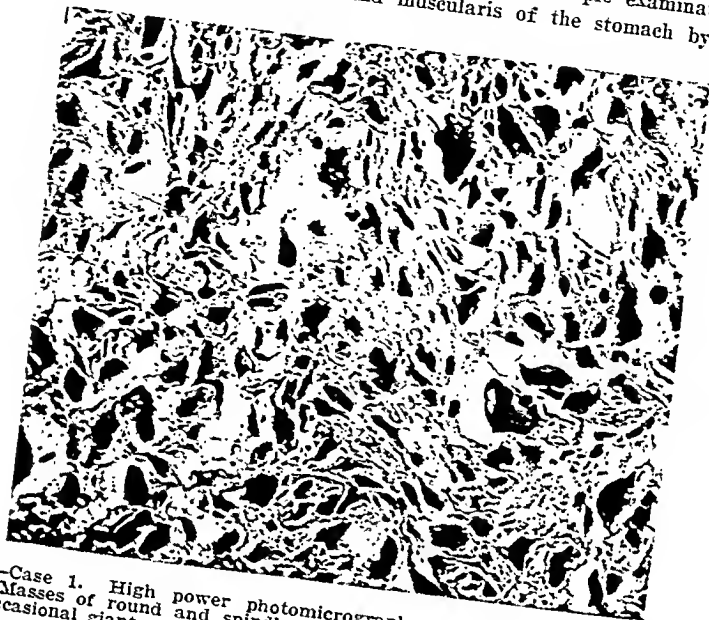


Fig. 1.—Case 1. High power photomicrograph of spindle-cell sarcoma of the stomach. Masses of round and spindle cells are supported by an abundant fibrous stroma. Occasional giant cells with two nuclei occur.

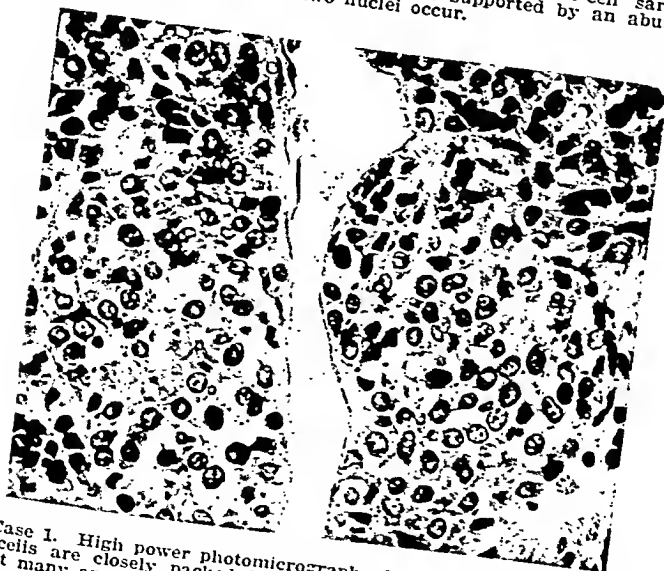


Fig. 2.—Case 1. High power photomicrograph of a metastatic deposit in the liver. The tumor cells are closely packed in a scant fibrous stroma. Most of them are polygonal but many are spindle-shaped. Occasional mitotic figures occur.

round and spindle-shaped cells supported by an abundant fibrous stroma. There were also occasional giant cells with two nuclei. The tumor cells possessed an abundant hyaline pink cytoplasm and round or oval, deeply staining nuclei. The tumor cells of the liver deposits were closely packed in a scant fibrous stroma. Most of them were polygonal with abundant cytoplasm but many were spindle-shaped. Occasional mitotic figures were seen. A diagnosis of spindle cell sarcoma was made.



Fig. 3.—Case 2. Roentgenogram showing a large filling defect in the upper portion of the greater curvature of the stomach. This evidence was not sufficient for positively determining the site of origin of the tumor.

CASE 2.—G. G., male, aged 62 years, was seen July 27, 1938. He had felt well until the last five weeks when, at first, his appetite failed and weakness developed. Soon a moderate weight loss of eight to ten pounds occurred. He continued to work for three weeks. Ten days before admission pain was first complained of. It appeared after he had retired as a quite severe colic just to the left of the umbilicus. It continued during the whole night. A physician was called. There was no special examination and no treatment was instituted. Ten days later, which

was the day he entered the hospital, he had a second attack of abdominal pain which was similar to the first. The family physician this time felt a tumor. At no time had there been nausea, vomiting, or any noticeable disturbance of the stools. The only noteworthy physical findings were evident weight loss and a large, firm, nodular mass in the left hypochondrium. It moved with respiration and was not tender. Hemoglobin was 80 per cent; erythrocytes, 4,540,000; leucocytes, 13,700; differential count, normal. One stool examination showed no occult blood. Roentgenologic examination after a barium meal showed a large filling defect in the upper portion of the greater curvature of the stomach. Some of the barium spread out over the region of the palpable mass and here the rugae were seen to be widely spaced.



Fig. 4.—Case 2. Photograph of the resected gastric segment involved by the sarcoma together with the attached spleen.

Movement of the mass shifted the stomach and indicated an attachment between the two. Normal peristaltic waves were seen in the lower third of the stomach. There was no gastric residue at the end of six hours. This roentgenologic evidence was not sufficient for determining positively the site of origin of the tumor; it was thought, however, to arise in the stomach. A preoperative diagnosis was made of a tumor probably primary in the stomach but of undetermined type. Through an upper left rectus incision on Aug. 5, 1938, an enormous nodular tumor mass was exposed. All of the surrounding viscera were firmly and extensively adherent to it; particularly was this true of the spleen. The tumor was found to arise from the greater curvature of the stomach and to be resectable. A sleeve type of re-

section, which included the adherent spleen, was performed. An uneventful recovery followed. The patient gained twenty-eight pounds and felt well during the following eight months. At this time roentgenologic examination after a barium meal showed nothing abnormal except a small stomach. Soon afterward he began to fail. He was next examined eight months later, which was sixteen months after he was first seen and operated upon. A tumor was palpated at the site of the first mass and x-ray examination revealed evidence of a recurrence in the stomach. A second operation on Nov. 17, 1939, confirmed these findings. Several metastatic deposits were observed in the liver. The immediate convalescence from the exploratory laparotomy was uneventful. Death occurred two months later.

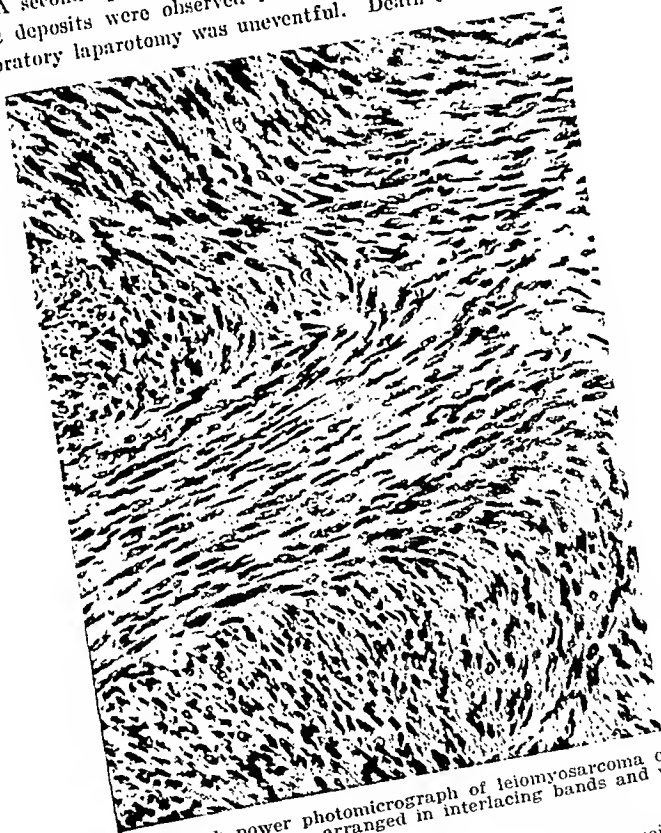


Fig. 5.—Case 2. High power photomicrograph of leiomyosarcoma of the stomach. Masses of spindle-shaped cells are arranged in interlacing bands and whorls. Mitotic figures are abundant.

The mass removed at the first operation, including the spleen, weighed 2150 Gm. It measured 20 cm. long, 16 cm. wide, and 13 cm. thick. The spleen was normal in size. The tumor was found to be of gastric origin. The stomach mucosa over it was intact. The muscularis was completely infiltrated by the growth. A central cyst 10 cm. in diameter was found to contain necrotic tumor tissue. The whole tumor was nodular. Microscopic examination revealed masses of spindle-shaped cells arranged in interlacing bands and whorls. The nuclei were oval, varied considerably in size, and contained a finely granular scattered chromatin. The cytoplasm was abundant. Mitotic figures were abundant. Morphologically the cells suggest those of smooth muscle origin. The tumor was seen to arise in the muscularis of the stomach. Its mucosa covering was very thin but intact. *Diagnosis:* Leiomyosarcoma of the stomach. No evidence of metastases was found at the first operation or upon subsequent examination of the tissue removed.

TABLE I

CASE REPORTS OF PRIMARY SARCOMA OF STOMACH COLLECTED FROM LITERATURE SINCE 1930

AUTHOR	NO. OF CASES	AUTHOR	NO. OF CASES
Askey, Hall, and Davis	1	Hunt	1
Balabon	1	Husted	1
Barzell	1	Iacobovici and Stoia	1
Basso	1	Johnson et al.	1
Baumgartner	1	Jones and Carmody	1
Blasi	1	Jordan	1
Brereton	1	Karpe	1
Brocai	1	Klimko	1
Bukowski	1	Lawson	1
Cabot Case 18262	1	Lefort	1
Cabot Case 19222	1	Matyas	1
Cabot Case 19372	1	Melnick	1
Cabot Case 19401	1	Mendelson	1
Cabot Case 20471	1	Middleton	2
Cabot Case 21112	1	Pack and McNeer	7
Cabot Case 23312	1	Pattison	2
Cabot Case 23512	1	Phillips	2
Cabot Case 24501	1	Phillips and Adam	1
Cardillo	2	Phillips and Kilgore	1
Case	1	Pick	1
Cazzamali	1	Ransohoff and Dickson	2
Cheever	1	Reeves	2
Clar	1	Reutschler and Travis	1
Collins	1	Roffo and Gondolfo	1
Collins and Carmody	2	Romeo	1
Comando	1	Schiff and Foulger	1
Counsellor and Collins	1	Schultz	1
D'Aunoy	4	Shioda	1
Drane	1	Singer	1
Edwards and Wright	1	Spitzenberger	1
Fedorow	1	Suck	1
Fiessinger and Bergeret	1	Taylor	5
Forbes	1	Venable	1
Freeman	1	Voeckler	4
Glenn and Douglas	1	Wagner	2
Golob	1	Walters and Church	1
Gosset et al.	1	Yardumian	2
Hameed	1	Zellhoefer	1
Harney	1	Zoph et al.	1
Howard and Speer	1		

According to current opinion 1 to 2 per cent of all primary gastric malignancies are nonepithelial tumors. There are approximately 400 case reports in the literature, of which more than one-fourth have been published during the last ten years.

Nonepithelial tumors of the stomach do not all reveal histologic evidence which is final concerning their malignancy. Malignant forms are occasionally confused with anaplastic carcinomas.

Benign tumors not infrequently and carcinomas only occasionally, therefore, may be erroneously included in this as well as in all other such collections.

Confusing terminologies and classifications reveal the unsettled state of this subject among pathologists. We are not concerned here with these controversial matters, which for the most part are of academic interest

section, which included the adherent spleen, was performed. An uneventful recovery followed. The patient gained twenty-eight pounds and felt well during the following eight months. At this time roentgenologic examination after a barium meal showed nothing abnormal except a small stomach. Soon afterward he began to fail. He was next examined eight months later, which was sixteen months after he was first seen and operated upon. A tumor was palpated at the site of the first mass and x-ray examination revealed evidence of a recurrence in the stomach. A second operation on Nov. 17, 1939, confirmed these findings. Several metastatic deposits were observed in the liver. The immediate convalescence from the exploratory laparotomy was uneventful. Death occurred two months later.

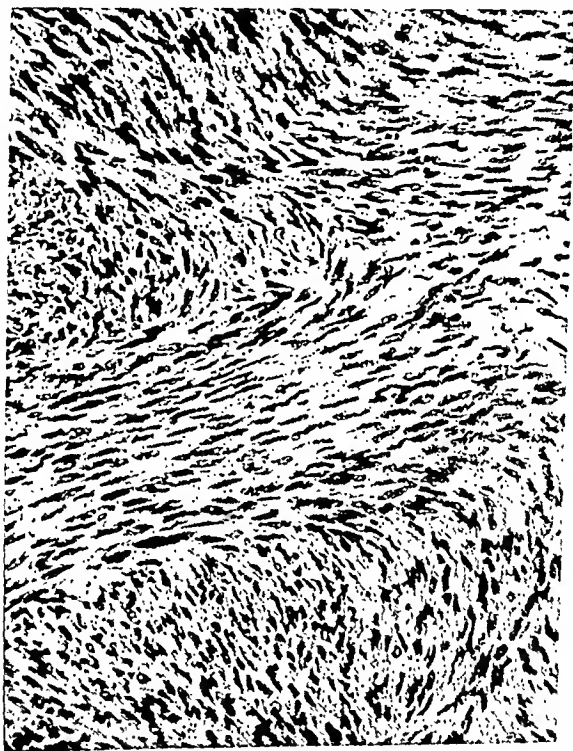


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cell differentiation. Clinically and surgically, however, they are indistinguishable and, therefore, are considered here as one inseparable class in which are found thirty-nine of the 104 collected cases.

Sex incidence is not noteworthy. The average age at the time of hospital admittance was 48.4 years. The youngest patient was 13 years of age and the oldest 70 years old. About three-fourths of the cases were in their fifth, sixth, and seventh decades.

For the most part these spindle-cell sarcomas when seen at operation or autopsy are large or massive bulky growths which protrude outwardly to a very marked degree in about one-half the cases and considerably less often project within the gastric lumen to form respectively the so-called exo- and endogastric masses. The former attain the largest size of any stomach tumors. They are occasionally described as being as large as a fetal or an adult head and very exceptionally may weigh as much as 6,000 Gm. Spindle-cell sarcomas of small size are rarely seen. Pedunculated attachments are not infrequent and usually involve only a few square centimeters of stomach wall even when the tumor itself is of enormous size. Growth is by expansion, encapsulated for the most part, and seldom by infiltration or invasion. In extending beyond the stomach at the curvatures these exogastric tumors very often penetrate between the leaves of the gastrocolic and gastrohepatic omentum.

Any part of the stomach may be the site of origin. The proximal divisions seem to be most frequently involved. The orifices, oftener the cardiac, are occasionally encroached upon but rarely if ever obstructed, due in large part, no doubt, to the absence of an annular arrangement. Multiple growths are rare.

Since these tumors arise from the deeper layers of the gastric wall, involvement of the mucosa and serosa, which is frequent, is always secondary. Sooner or later the mucosa overlying these tumors usually becomes involved by single or multiple ulcers which give rise to the bleeding which complicates over one-half of these usually very vascular tumors. This bleeding is often intermittent over a period of months and years and is usually considerable or massive. The serosal surfaces are frequently extensively adherent to the surrounding viscera and peritoneal surfaces.

Extensive degenerative changes occur in a large percentage of the growths to form hemorrhagic and necrotic single or multiple cysts which sometimes become infected and abscessed. These cystic changes of stomach sarcomas are apparently limited to the spindle-cell variety. Deep sinus tracts may extend from the gastric lumen into the degenerated tumor. Necrosis may be extensive but seldom leads to perforation.

Metastases are noteworthy because of their relative infrequency and apparent predilection for the liver. Only 8, or 20.5 per cent, of these tumors gave rise to secondary deposits which were found in the liver as well as elsewhere in 7 instances. Metastasis to the right lung in 1 case constituted the only instance of an extra-abdominal occurrence.

only. We have employed, therefore, a simple classification and have centered our attention chiefly upon the two large tumor groups to which nearly all belong; namely, the spindle-cell sarcomas and the malignant tumors of lymphoid origin.

Twelve tumors, probably all of lymphoid origin, were reported as round-cell sarcomas and because of this have been given a separate classification here, without, however, a description separate from that for the tumors of lymphoid origin.

Six other tumors are likewise grouped together for reasons which will be revealed later.

TABLE II

	SPINDLE-CELL SARCOMAS		MALIGNANT TUMORS OF LYMPHOID ORIGIN		ROUND-CELL SARCOMAS		UNCLAS-SIFIED		TOTAL NO.	
No. Sex	Males	Fe- males	Males	Fe- males	Males	Fe- males	Males	Fe- males	Males	Fe- males
Average age	22	17	33	14	8	4	4	2	67	37
No. operable	48.4		42.5		39.5		42.33		44.3	
Percentage operable	29		31		10		4		74	
	74.33		64.7		83.3		66.6		71.7	
Gastric resection	19		30		10		3		62	
Excision	10		1		0		1		12	
Operative fatalities	3		7		1		0		11	
Percentage of operative fatalities	15.7		22.5		10		0		14.8	
No. explored without removal of tumor	5		11		0		2		18	
No. and percentage of exploratory operative fatalities	4		5		0		1		10	
	80 %		45.5%		0 %		50 %		55.5%	
No. and percentage of unoperated cases (all died soon after examination)	5		5		2		0		12	
	12.8 %		10.6%		16.6%		0 %		11.5%	
No. treated by radiation alone, all after exploratory laparotomy	1		4		0		0		5	

The spindle-cell sarcomas arise from smooth muscle and connective tissue of the ordinary and perineural variety and include the tumors usually referred to as leiomyosarcoma, fibrosarcoma, and neurogenic fibrosarcoma. Among other names in current use for these same tumors are malignant leiomyoma, myosarcoma, myogenic sarcoma, myoblastic sarcoma, fibroblastic sarcoma, fusocellular sarcoma, fibrosarcoma of neurogenic origin, and malignant Schwannoma. Not infrequently a histologic distinction cannot be made between these varieties of spindle-cell tumors, particularly in instances of rapid growth and incomplete

all other collections are the malignant tumors of lymphoid origin which here number 47, or 45 per cent of the total. About three-fourths of them are diagnosed lymphosarcomas, while the remaining bear such names as malignant lymphoma, malignant lymphoblastoma, malignant lymphocytoma, reticulum cell sarcoma, and lymphogranuloma or Hodgkin's disease. While microscopic differences do exist within this group, it is a question how far one should go in expressing these differences in his terminology. The considerable confusion which exists is due not alone to a multiplicity of names but to a lack of uniformity in meaning of the same name when used by different authors or by the same author at different times. Whatever may be the final decision as to whether or not all the tumors in this group represent the same underlying disease process and whether or not the histologic differences noted are of more than academic interest, we believe that the evidence now available justifies for our purpose considering them as an undivided group. Males predominate better than two to one. The average age was 42.5 years. The youngest patient was 3 years and 8 months old and the oldest was 72 years old. Few such tumors occur in the first and eighth decades, but they are found fairly well distributed throughout the intervening decades with a preponderance in this collection in the third and sixth.

They are for the most part single, flattened, diffuse, infiltrative masses which arise from the deeper layers of any part of the stomach, most frequently, however, on the lesser curvature and in the distal third which contained a part or all of the tumor in two-thirds of this collection. Saddle formations at the curvatures with extension to both walls is the rule and single wall involvement the exception. Twenty to twenty-five per cent of the tumors are annular and as such occur in most instances at the pylorus, producing, along with other stenosing types wherever located, an occasional obstruction, which is seldom high grade.

The large size which these tumors occasionally attain is usually due to a more or less uniform or nodular thickening of a large part of the stomach, and less often to a massive projection from a more or less limited area. Exogastric and endogastric lymphoid sarcomas are therefore infrequent and very rarely, if ever, pedunculated. Infrequently leather bottle types and small sharply circumscribed tumors occur.

The overlying mucosa is commonly invaded by tumor cells. Ulceration occurs in over one-half the cases and is frequently superficial but extensive and only occasionally craterlike and deep. About one-third of the tumors bleed. Hemorrhages are large or massive in about one-half of them, and only a few bleed intermittently.

The serosa is invaded in less than one-third of the cases with adherence usually to adjacent surfaces.

The central degenerative changes so common in the spindle-cell type were not mentioned in a single instance among these 47 sarcomas of

TABLE III  
LOCATION OF METASTASES

	SPINDLE-CELL SARCOMAS (8)	MALIG- NANT TUMORS OF LYMPHOID ORIGIN (19)	ROUND- CELL SARCOMAS (3)	UNCLAS- SIFIED SARCOMAS (2)	TOTAL SARCOMA CASES (32)
Regional lymph nodes	2	15	2	1	20
Liver	7	1	0	0	8
Retroperitoneal lymph nodes	1	3	1	0	5
Mesenteric lymph nodes	0	1	0	1	2
Lung	1	1	0	0	2
Spleen	0	3	0	0	3
Diaphragm	0	2	0	0	2
Pancreas	1	2	0	0	3
Gall bladder	1	0	0	0	1
Appendix	1	0	0	0	1
Peritoneum	1	0	0	0	1
Ureter	0	1	0	0	1
Inguinal lymph nodes	0	1	0	0	1
Peritoneal lymph nodes	0	1	0	0	1
Pelvic lymph nodes	0	1	0	0	1
Supraclavicular lymph nodes	0	1	0	0	1
Epicardium	0	1	0	0	1
Medullary cavity long bones	0	1	0	0	1

While radiation is very effectively applied to sarcomas of the stomach of lymphoid origin, it has found practically no place in the treatment of the spindle-cell type. Surgical extirpation by resection or excision is the only curative procedure practiced and was employed in 29 of these 39 cases, which gives an operability of 74.3 per cent. Three, or approximately 10 per cent, suffered operative fatalities. Fifteen were followed for less than six months, if at all. Only 5 were reported to be living and well for a year or more postoperatively and only 1 of all these 39 cases of spindle-cell sarcoma was reported to be living and well longer than five years. These extremely poor results may be more apparent than real in view of the high percentage of incomplete reports. In spite of this they are noteworthy, particularly because of the actual and relatively high percentage of operability of tumors of low-grade malignancy.

The largest division of sarcomas of the stomach in this as well as in

TABLE IV  
CASES WITH KNOWN METASTASES AT OPERATION OR AUTOPSY

	SPINDLE- CELL SARCOMAS (39)	MALIG- NANT TUMORS OF LYMPHOID ORIGIN (47)	ROUND- CELL SARCOMAS (12)	UNCLAS- SIFIED SARCOMAS (6)	TOTAL NO. OF CASES (104)
No.	8	19	3	2	32
Percentage	20.5	40.4	25	33.33	30.7

TABLE V

RESULTS AFTER SURGICAL REMOVAL OF 74 OF 104 STOMACH SARCOMAS

	SPINDLE- CELL TYPE	LYMPHOID- CELL ORIGIN	ROUND- CELL TYPE	UNCLAS- SIFIED	TOTAL NO.
Operative fatality	3	7	1		
Survival under 6 mo.	11*	5	3	0	11
Survival 6 mo. to 1 yr.	3	2	2	1	20
Survival 1 to 5 yr.	4	4	2	2	9
Survival 5 to 10 yr.	1	3	1	1	10
Survival 10 to 15 yr.	0	0	0	0	4
Survival 15 to 20 yr.	0	1	1	0	1
Insufficient information	4	5*	0	0	1
Living but not well under 6 mo.	0	1	0	0	9
Died under 1 yr.			1	0	2
Died under 2 yr.	1	2†			
Died under 3 yr.	1	1†	1	0	4
Total No.	1	0	0	0	2
	29	31	10	4	74

\*One had postoperative x-ray therapy.

†Had postoperative x-ray therapy.

Two-thirds of the round-cell sarcoma cases were males and their average age was 39.5 years. Three were in the second and four in the sixth decades.

Ten, or 83.5 per cent, were operable and underwent some kind of gastric resection with 1 operative fatality. Only 2 were reported to be living and well a year or longer after operation, 1 for three and 1 for eleven years, in none of whom metastases were encountered.

The 6 remaining tumors bear the following designation: sarcoma, mixed-cell sarcoma, liposarcoma, angiosarcoma, and mesothelioma. There were 4 males and 2 females. The average age was 42.3 years. The one designated only as sarcoma and the two mixed-cell sarcomas resembled tumors of lymphoid origin; whereas, the other three resembled spindle-cell types. All were operated upon and the 2 with evident metastases were simply explored. Four of the tumors were removed, 3 by resection

TABLE VI

RESULTS IN 5 CASES OF SARCOMA OF STOMACH RECEIVING RADIATION THERAPY ALONE

	SPINDLE- CELL TYPE	LYMPHOID- CELL ORIGIN	ROUND- CELL TYPE	UNCLAS- SIFIED	TOTAL NO.
Living and well 2 mo.	1	0	0	0	1
Living and well 14 mo.	0	1	0	0	1
Living and well 5 yr.	0	1	0	0	1
Living but not well 6½ yr.	0	1	0	0	1
No information	0	1	0	0	1
Total No.	1	4	0	0	5

lymphoid origin. There were 4 instances of perforation in 3 individuals; in 1 with recurrent perforation this complication followed soon after x-ray therapy.

Metastases are about twice as frequent as in the spindle-cell type, occurring in 40.4 per cent. With three exceptions they were limited to the abdomen, usually to the regional lymph glands.

Thirty-one, or approximately two-thirds, of the tumors were operable. Twenty-nine were removed by some form of gastric resection and 1 by excision. A first stage fatality prevented removal in one instance. Seven, or 22.5 per cent, of these 31 cases suffered operative fatalities. Eleven were followed for six months or less, if at all. Eight, or 25.8 per cent, were living and well for a year or more postoperatively and one-half this number for five years or longer. Metastases were encountered in only 1 of these 8 survivors; he was living and well three years postoperatively and had had no radiation therapy. Radiation in the form of postoperative x-ray therapy was given to only 1 of these 8 cases; it was given in the absence of any known metastases and with a known survival period of one and one-half years. These facts alone, therefore, do not warrant any conclusions for or against postoperative radiation therapy in the treatment of this kind of malignancy. Malignant tumors of lymphoid origin, however, are known to be, as a rule, sensitive to radiation and positive proof of this is found in 4 of the 11 tumors which were surgically hopeless at operation. Radiation therapy alone resulted in 1 apparent six-year cure and 2 satisfactory survivals of more than one year. A fourth survivor was living but not well for six and one-half years. His is a most interesting case. At operation there was found, in addition to an apparently hopeless reticulum-cell sarcoma of the stomach, a perforation of the same which was closed. Inadequate x-ray therapy is stated to have been given postoperatively and to have been repeated one year later in a series of ten treatments. Soon afterward a second perforation occurred near the site of the first and was successfully treated surgically. One is justified in suspecting that the second perforation may have resulted from a softening of the malignant stomach lesion incident to the radiation which was received, since such complications in hollow viscera under these circumstances have been known to occur. Because of this danger some radiologists prefer to radiate such cases after the removal of the primary growth rather than before.

From these data we learn that 6 of 47 (12.7 per cent) cases with malignant stomach tumors of lymphoid origin survived for five years or longer after the institution of treatment, which consisted of surgical removal alone in four instances and of radiation alone in 2 instances. These results, while not good, are much better than in the spindle-cell variety and support the contention that the greatest percentage of five-year survivals is found among the tumors of lymphoid origin which are judged the most malignant.

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### SUMMARY

Primary malignant nonepithelial stomach tumors comprise about 1 to 2 per cent of all gastric cancers. Most of them are either spindle-cell sarcomas of connective tissue or smooth muscle origin or tumors which arise from lymphoid tissue. Round-cell sarcomas of smooth muscle and connective tissue origin and angiosarcomas occur less frequently.

The degree of malignancy of the spindle-cell type is low. The operability of both groups is notably high. Radiation therapy is very effective in some of the tumors of lymphoid origin.

In spite of these several factors which are very favorable for cure, the results of treatment in both groups are very disappointing.

Of 104 collected and 2 personally observed cases, there were 6 five-year survivals, 1 among 41 with spindle-cell sarcomas, and 5 among 47 with malignant tumors of lymphoid origin.

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## CISTERNAL ENCEPHALOGRAPHY

### UTILIZATION OF SPONTANEOUS FILLING OF VENTRICLES WITH AIR FOLLOWING WITHDRAWAL OF FLUID BY CISTERNAL PUNCTURE

RICHARD H. YOUNG, M.D., OMAHA, NEB.

IN 1932 Schaltenbrand<sup>1</sup> called attention to the fact that cerebrospinal fluid withdrawn by cisternal puncture, with the patient in the sitting position, allowed the spontaneous introduction of air into the ventricles. This observation was utilized by Schaltenbrand in the development of a method of encephalography that allowed the use of a small amount of air (30 to 40 c.c.) and was designated by him as the "small" cisternal encephalogram. This procedure has been utilized to a considerable extent in Germany and in Scandinavian countries but has had little use in America. According to Schaltenbrand, this method is indicated in cases of progressive cerebral disease without marked increase of intracranial pressure other than epilepsy, suspected cortical atrophy, and suspected pachymeningitis. The method was described as contraindicated in marked arteriosclerosis and marked increase in intracranial pressure.

The use of this procedure in twenty-two cases over a period of the past year has allowed the employment of this method in a variety of cases and provides the experience on which this paper is based.

#### METHOD

In the patient without increase in intracranial pressure the cisternal pressure is approximately 0 in the sitting position. The withdrawal of cerebrospinal fluid creates a negative cisternal pressure, causing air to be drawn through the needle into the subarachnoid space until the pressure is again atmospheric. As a result, the only equipment needed is a 10 c.c. syringe to withdraw the cerebrospinal fluid from the cistern.

**Medication:** Two hours before the encephalogram sodium amytal, 0.2 Gm., is given by mouth. Twenty minutes before morphine sulfate, 0.010 Gm., and scopolamine, 0.0003 Gm., are given hypodermically.

The patient is placed in a sitting position, either in bed or in a special chair, such as is used for lumbar encephalography. A nurse, with a hand on either side of the head, maintains its proper position of slight flexion of the neck. After proper preparation of the puncture site a cisternal puncture is made in the usual manner. Because of the lack of spontaneous flow of cerebrospinal fluid, special care must be exerted during the puncture, the syringe attached to the needle, and attempts made to withdraw fluid. When cerebrospinal fluid is obtained, 10 c.c. is slowly withdrawn and the syringe then disconnected from the needle. By listening closely, air can be heard bubbling through the

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lower left facial weakness. Motor reactions showed a mild left hemiparesis. There was an increase in the deep reflexes on the left, with ankle clonus and a left Babinski response. There was an uncertainty in the left finger-to-nose test, but no true ataxia. There was a decrease in position sense on the left, with astereognosis.

A lumbar puncture was done and was said to have shown a normal pressure and dynamics. The cell count was 3; globulin, negative; Wassermann, negative; colloidal gold curve, 0000000000.

A small cisternal encephalogram was done on Dec. 13, 1939, at which time 18 c.c. of cerebrospinal fluid were withdrawn. The x-ray report revealed no air in the right ventricle, but the left lateral ventricle and the third ventricle were displaced to the left (Fig. 1). A diagnosis of a deep-seated right parietal tumor was made and operation was advised.

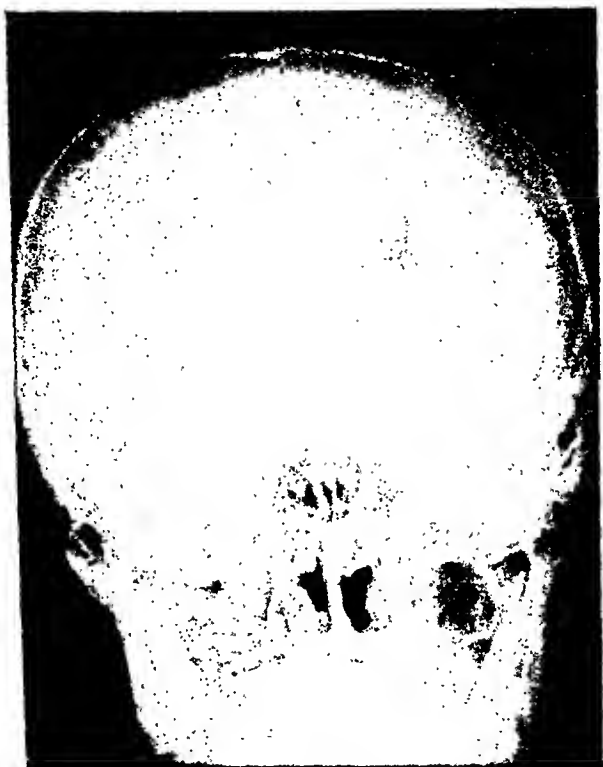


Fig. 1.—Case 1. Visualization of displaced left lateral ventricle, after withdrawal of 18 c.c. of cerebrospinal fluid.

On Dec. 21, 1939, an osteoplastic flap over the right parietal area was made by Dr. L. D. McGuire. The tumor was classed as inoperable, a decompression was done, and the patient was returned to his room. On the following morning, the patient died.

At the post-mortem a tumor was encountered in the extreme posterior end of the parietal bone flap. The tumor was covered by about 2 mm. of cortex, was approximately 4 cm. in diameter, and extended about 4 cm. into the brain substance. The location was in the posterior parietal region and did not extend into the occipital lobe. The entire right cerebral hemisphere was markedly enlarged and edematous. The lateral ventricle was almost obliterated by the marked edema. The pathologic report of the tissue was spongioblastoma multiforme.

needle as it is being drawn into the cistern. When air no longer can be heard passing through the needle, the syringe is again connected to the needle and 10 c.c. more of cerebrospinal fluid is withdrawn. This procedure is repeated until the desired amount of fluid (usually 30 to 40 c.c.) has been obtained.

Immediately following the removal of the needle from the cistern, appropriate roentgenograms are taken. With the small amount of air used, it is necessary to take films in the horizontal as well as in the vertical position. It is only in the horizontal position that the temporal horns may be visualized.

#### OBSERVATIONS

In the majority of cases in which this method of encephalography was performed, the procedure was utilized to differentiate brain tumor from an inflammatory or degenerative disease of the cerebrum. In no case was the cerebrospinal fluid pressure over 20 mm. of Hg or 250 mm. of water. While the usual procedure was to withdraw 30 to 40 c.c. of cerebrospinal fluid, it was possible to obtain very informative encephalograms with the withdrawal of as little as 15 c.c. in certain cases of brain tumor.

With the use of this method there was not the degree of distress or shock that is associated with lumbar encephalography. Headache, while present, was not severe, vomiting was rare, and there has been little change in the state of consciousness. A significant lowering of the pulse rate has been infrequent and profuse perspiration with pallor has been rarely encountered.

There has been a failure of the ventricles to fill in one case. This patient had a right frontal cystic astrocytoma which was verified by operation at the Mayo Clinic. At the time of cisternal encephalography only 12 c.c. of cerebrospinal fluid could be obtained, and this with difficulty. The x-ray examination showed air in the posterior fossa over the surface of the cerebellum. It has been Schaltenbrand's experience that in those cases where there was a failure of the ventricles to fill with cisternal encephalography a similar failure resulted when encephalography was repeated by the lumbar method.

The type of case in which cisternal encephalography was employed and the results obtained may be illustrated by the presentation of three case reports.

CASE 1.—B. T., a 47-year-old druggist, had been well until four weeks prior to his admission to St. Joseph Hospital on Nov. 27, 1939. The hospital record stated that four weeks before he had contracted influenza and had failed to show a good recovery, in that he continued to lose weight and strength. Because of the complaints of headaches, difficulty in concentration, and nervousness, he had been advised to consult a psychiatrist. Two weeks before admission there developed urgency and precipitancy of urination. Shortly thereafter, there was a slowly progressing left-sided weakness.

This patient was seen in consultation with Dr. G. W. Dishong, and on examination the cranial nerves showed a slight blurring of the optic disks and a slight

two sides. Superficial reflexes were all normal in type. Coordination tests were well performed, although there was some unsteadiness in the right heel-to-knee test. Sensory status showed normal appreciation of all types of sensation.

X-rays of the skull showed the anterior clinoid on the left to be slightly decalcified; the pineal body was shifted 5 mm. to the right and 5 mm. posteriorly.

A cisternal encephalogram was done, with the withdrawal of 16 c.c. of fluid. The cisternal encephalogram showed the ventricles shifted to the right, with apparent compression from the inferior and lateral sides of the left lateral ventricle, which was incompletely filled (Fig. 2). The third ventricle was not visualized. There was no evidence of air in the subarachnoid spaces over the hemispheres.

From the neurologic examination and the cisternal encephalogram, it was felt that there was a tumor in the left central parietal region.

On Sept. 6, 1939, a craniotomy was done by Dr. J. J. Keegan. A large oval pedicle flap was made over the left parietal region. At about 3 cm. depth in the left temporal parietal region a brain tumor was exposed and partially removed. A microscopic section of the tissue removed at the time of operation was diagnosed as astroblastoma.

*Comment.*—In this case the neurologic findings pointed to a left temporal parietal tumor. This was confirmed by the withdrawal of a small amount of fluid (16 c.c.) from the cistern, which showed a compression of the left lateral ventricle and a shift to the right.

CASE 3.—P. C., a 36-year-old business man, was seen Aug. 3, 1939, because of dimness in vision. Nine years before he first had noticed failing vision in his left eye. At that time he was found to have a beginning optic atrophy in the left eye with a gross defect in the lower visual field. A cisternal puncture showed normal pressure, no cells, a protein at the upper limit of normal, and a negative Wassermann test. It was suggested that he might have an early multiple sclerosis. Subsequently, there was little change in vision until June, 1939, when there was an additional blurring in the right eye.

The history by systems was negative and the general physical examination was likewise negative.

The neurologic examination at this time showed a left optic atrophy and a slight papilledema on the right. Otherwise, the neurologic examination was negative.

A cisternal encephalogram was done, with the withdrawal of 50 c.c. of spinal fluid. X-ray films revealed that the ventricles were slightly enlarged, but normal in contour (Figs. 3 and 4). There was no apparent displacement of the median line structures. There was some filling of the subarachnoid spaces in the frontal area. The patient experienced no distress from this procedure and insisted on making a 150-mile drive to his home the following day.

*Comment.*—The cisternal encephalogram was of diagnostic value in this case which presented a Foster Kennedy syndrome. The encephalogram made it possible to differentiate between an inflammatory disease and a subfrontal tumor. It is also remarkable that this man experienced little distress and insisted upon driving to his home, 150 miles away, the following afternoon.

#### COMMENT

Davidoff and Dyke<sup>2</sup> stated that good results in lumbar encephalography may be obtained with 70 c.c. of air. As little as 20 c.c. have

*Comment.*—In this case there was originally the question of whether the neurologic disability was due to a tumor or to a degenerative disease. The withdrawal of only 18 c.c. of fluid allowed the introduction of sufficient air to detect a ventricular shift. No air was seen in the right lateral ventricle, but at autopsy the right ventricle was found to be almost obliterated by a massive edema which involved the whole right hemisphere.



Fig. 2.—Case 2. Visualization of compressed and displaced left lateral ventricle (A) after withdrawal of 16 c.c. of cerebrospinal fluid.

CASE 2.—E. R., a 28-year-old farmer, entered the University Hospital Aug. 13, 1939, complaining of headaches for one month, dimness of vision for two weeks, and forgetfulness.

The history indicated he had been well until July 1, 1939, when he began to have headaches, which were chiefly frontal in location. Two weeks before coming to the hospital he had noticed ringing in both ears and seemed to experience difficulty in hearing. At about the same time he began to notice a dimness in vision and difficulty in seeing objects on his right. For the ten days prior to admission he had had severe headaches every day.

Past history, history by systems, and family history were not remarkable.

The neurologic examination revealed upper quadrant right homonymous hemianopsia in the cranial nerves. There was papilledema of 2 diopters on the left and of 1 diopter on the right. There was apparent reduction of hearing on the left. Motor status showed normal motor power, without tremor or disorder in tone. Reflex status showed the deep reflexes to be somewhat exaggerated, but equal on the

two sides. Superficial reflexes were all normal in type. Coordination tests were well performed, although there was some unsteadiness in the right heel-to-knee test. Sensory status showed normal appreciation of all types of sensation.

X-rays of the skull showed the anterior clinoid on the left to be slightly decalcified; the pineal body was shifted 5 mm. to the right and 5 mm. posteriorly.

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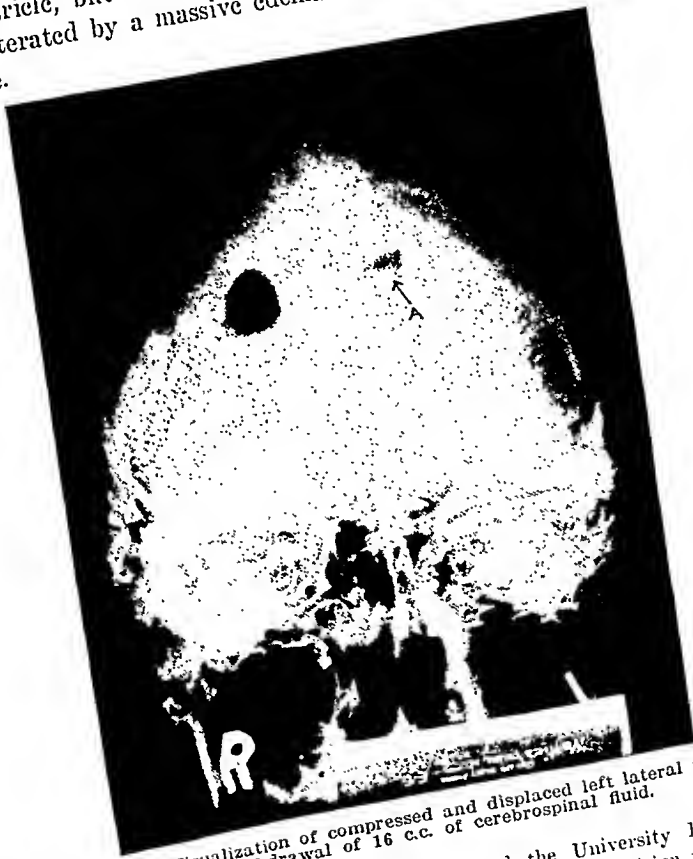


Fig. 2.—Case 2. Visualization of compressed and displaced left lateral ventricle (A) after withdrawal of 16 c.c. of cerebrospinal fluid.

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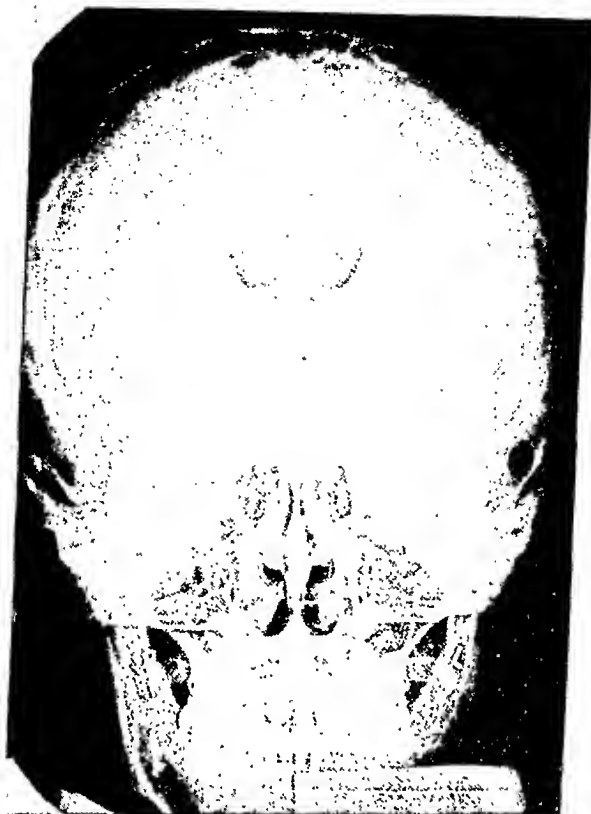


Fig. 3.—Case 3. Visualization of anteroposterior view following withdrawal of 50 c.c. of cerebrospinal fluid.

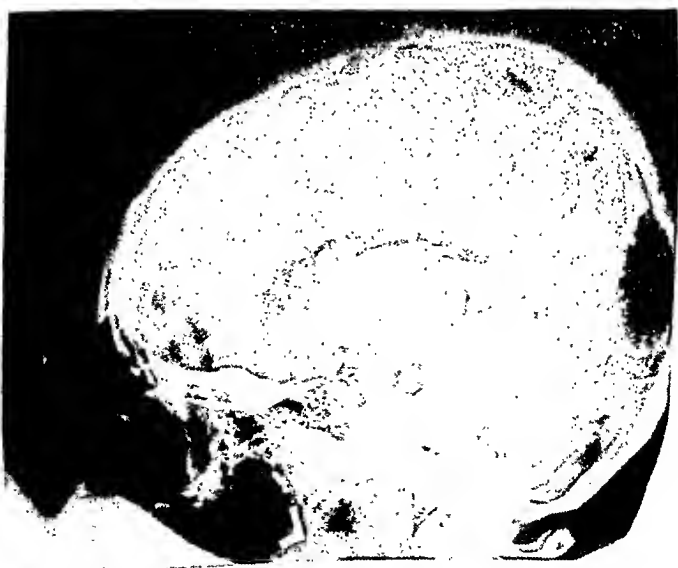


Fig. 4.—Case 3. Lateral view showing visualization of the anterior portion of lateral ventricles. No evidence of distortion suggesting tumor.

been used by Flügel,<sup>3</sup> and Davidoff and Dyke quote Cestan and Riser as using 30 to 40 c.e. Experience with the small cisternal encephalogram of Schaltenbrand would indicate that the withdrawal of 30 to 40 c.e. of spinal fluid allows the introduction of sufficient air to visualize adequately the ventricles, provided films are taken in a horizontal as well as vertical position.

This procedure has a definite appeal because of its simplicity in operation and the relative lack of distress or discomforting sequelae. These features allow a more general use of encephalography.

An attractive feature is that the final cerebrospinal fluid pressure in the cistern is the same in all cases (atmospheric). This provides a certain control that is not present in other methods of encephalography.

It is felt that the cisternal encephalogram reveals valuable information in cases of suspected brain tumor where the intracranial pressure is not remarkably elevated, and frequently the withdrawal of a small amount of cerebrospinal fluid (15 to 20 c.e.) is adequate.

There are definite limitations in the use of this procedure. It would seem that the chief contraindications would be (1) presence of a high degree of intracranial pressure, (2) suspected posterior fossa lesions, (3) signs of a cerebellar herniation with symptoms of neck stiffness and pain. There are perhaps some objections to the use of the cisternal puncture, based upon dangers such as have been described by Dandy.<sup>4</sup> This method would have little use in cases where the chief interest is the cortical pattern, such as epilepsy, because of the tendency of the air to enter the ventricular system before entering the subarachnoid spaces.

#### CONCLUSIONS

1. The method of cisternal encephalography of Schaltenbrand is described.

2. Experience with this procedure would indicate that it has a place as a diagnostic method where visualization of the ventricular pattern would aid in differentiating types of intracranial pathology.

3. The chief advantages of this type of encephalography are its simplicity, relative freedom from distressing symptoms, and the fact that the final cisternal pressure is the same in all cases.

4. The use of a small amount of air by this method would allow more general employment as a diagnostic aid.

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## AN AUTOLOCKING SILVER CLIP

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*(From the Department of Surgery, School of Medicine, Tulane University)*

IT HAS long been common knowledge that metallic silver is well tolerated by the tissues. Silver wire has been successfully employed as a suture material and for many years neurosurgeons have used silver clips for hemostatic purposes. The obvious advantage of using silver clips lies in their simple and effective application, particularly in situations in which the performance of ordinary ligation is difficult or practically impossible; also, their use permits considerable conservation of time and effort. However, these simple compressed folds of silver wire obviously cannot be employed upon large vessels. For this reason it would seem desirable to devise a silver clip which would assure a firm grip upon the tissue included in it and which could not open once it was applied. With this in mind an autolocking silver clip as described below has been devised.

The clip is made from thin ribbons of silver of varying widths and cut in varying lengths, depending upon the necessary size. The silver band is folded to form an angle of approximately  $45^{\circ}$ . One end is provided with a projecting tip approximately one-half the width of the silver band which is bent so as to point toward the opposite end (Fig. 1). This projecting tip acts as the locking device when the clip is closed. The clips are serrated on their inner surface to assure a firmer grip.

The clip applicator consists of a handle attached to long square rods which have jaws at their ends (Fig. 2). The square rods are so constructed that one slides within the other to produce opening and closing of the jaws. This is accomplished by the lever arrangement of one of the handles with the inner rod. The jaws are especially constructed with grooves into which the clip fits (Figs. 3 and 4). These grooves are approximately as deep as the clip is thick. In the lower jaw near the open end there is a second smaller, deeper, and narrower groove which is crescentic in shape and which serves the purpose of bending the projecting tip of the clip in the locked position when the jaws are closed (Figs. 3 and 4). Another groove is also present in the rod to which the lower jaw is attached (Figs. 3 and 4). This groove is approximately the width of the clip and serves the purpose of receiving the angled part of it so as to assure greater stability of the clip when fitted between the jaws. There is also a thin bandlike spring in this groove which presses against the angled part of the clip (Fig. 4). The purpose of this spring is to keep the clip firmly in place when fitted into the jaws and to expand with the greater length of the clip as it is pressed into the closed position, thus obviating buckling which would otherwise occur (Fig. 4).

The operation of the instrument is extremely simple. The silver clips are easily fitted into the grooves of the open jaws. They spring in readily by being slipped backward from the open end of the jaws. The ves-

sel or structure to be ligated is placed into the clip and the handles of the applicator compressed. As the jaws are forced into the closed position, the projecting tip of the clip fits into its corresponding groove on the lower jaw, which causes it to be bent around the lower end of the clip, thus automatically locking it (Fig. 4).



Fig. 1.—Photograph of an autolocking silver clip.

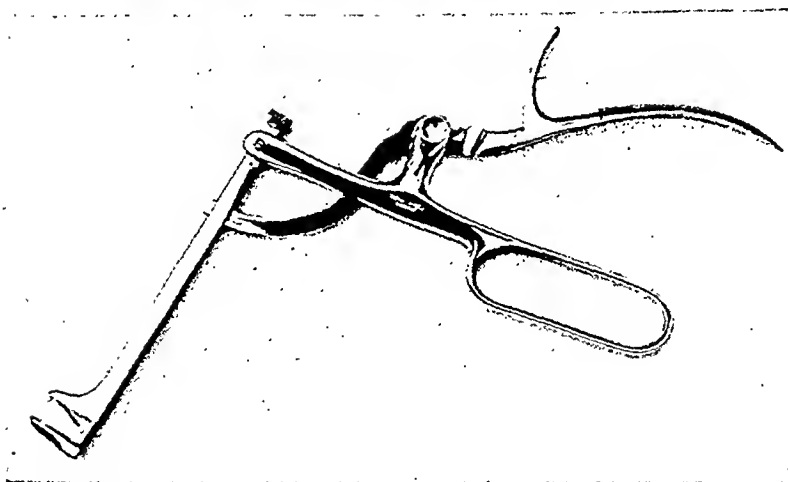


Fig. 2.—Photograph of an applicator containing an autolocking silver clip ready for use.

The clip has been applied experimentally in the performance of various types of operative procedures. Subsequent examination has revealed the clips intact, surrounded by fibrous tissue. Total pneumonectomy has been successfully performed in dogs using only the clips on the hilar vessels as well as on the bronchi and some of the animals are still living, almost a year after the operations were performed. The clip has even been applied to the abdominal aorta in dogs and in no case has it slipped off or failed to produce complete occlusion. No attempt will be made to give a detailed description of these experiments here as they will be presented in a subsequent report.<sup>1</sup>

The clinical application of such a clip is extensive and it is unnecessary to indicate its varied uses. Obviously it is desirable to have available various sizes of clips and corresponding sizes of jaws for their ap-

plication. Since a handle of only one size is necessary, the instrument is so constructed that the jaws can be easily detached from the handle and another size applied. The varying sized clips are made uniformly from lengths of silver ribbon by an especially constructed jig.

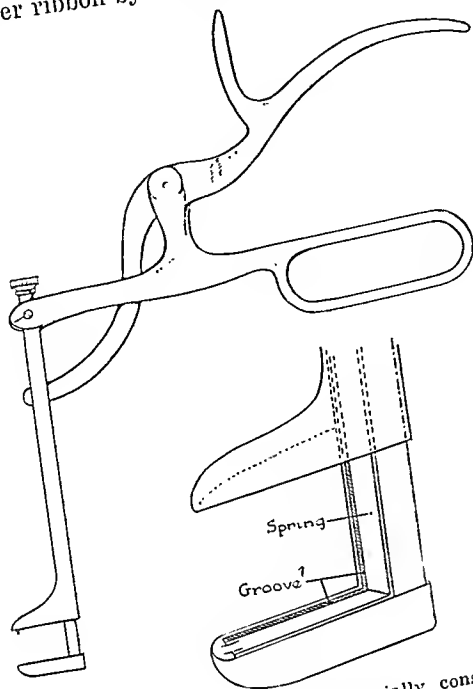


Fig. 3.—Drawing of the instrument showing especially constructed grooves in the jaws.

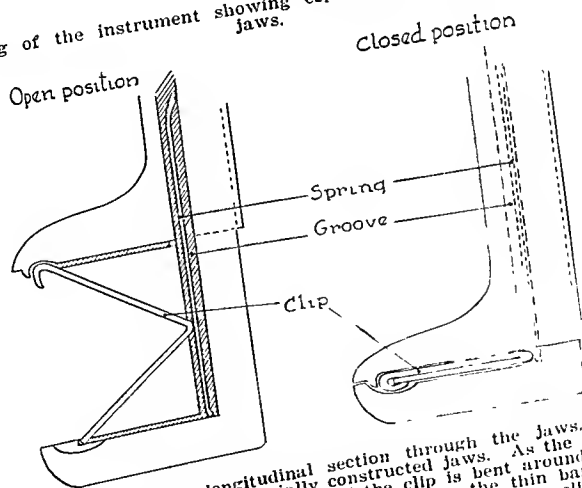


Fig. 4.—Drawing showing longitudinal section through the jaws. In the open position the clip is fitted into the especially constructed jaws. As the jaws are closed and the clip compressed, the projecting tip of the clip is bent around the lower end of the clip, automatically locking it. At the same time the thin bandlike spring is compressed backward to accommodate the greater length of the clip in the closed position.

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# Editorial

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## The Statistical Method

AT THE beginning of the sixth chapter of the *Anatomy of Science*, G. N. Lewis writes: "I am going to speak of the application of a kind of mathematics which, while based on arithmetic, occupies an independent position of great significance. It is a subject which should be taught in every elementary school, but the average educated man has no knowledge of it except that which he may have derived from a practice which society regards as vicious. I refer to the theory of probability, of which the elementary principles are of daily applicability."

While it is true that choice, chance, and probability had their origin in observations relative to gambling, their socially important uses today are in insurance, in dealing with all group phenomena, and in the reduction of scientific observations. Not only are they not taught in elementary schools, they are not taught today in the usual freshman and sophomore courses on mathematics in college, although thirty or forty years ago some account of them was often included in freshman courses on advanced algebra. The daily papers now print so much data from which inferences are drawn that some knowledge of statistics is really necessary to read the papers intelligently enough to avoid misinformation. The like is true of medical and public health professional journals to such an extent that not only the investigator who writes the articles but the practitioner who reads them should have some knowledge of probabilities; indeed, as many of the authors do not have sufficient knowledge of the subject to provide assurances for their inferences, the reader is under the unfortunate necessity of having some such knowledge himself or of having to accept or reject the conclusions quite blindly. One hesitates to urge that a curriculum so crowded as that of the medical schools should make place for a brief course on statistics, but the fact is that this has already taken place in some schools and seems likely to spread to others. Fortunately the elements of statistics are based directly on arithmetic, with only a modicum of school algebra, and are not so very hard to acquire, as Dr. Horace Campbell shows in this issue of the JOURNAL.

—E. B. Wilson, Ph.D.  
Boston, Mass.

plication. Since a handle of only one size is necessary, the instrument is so constructed that the jaws can be easily detached from the handle and another size applied. The varying sized clips are made uniformly from lengths of silver ribbon by an especially constructed jig.

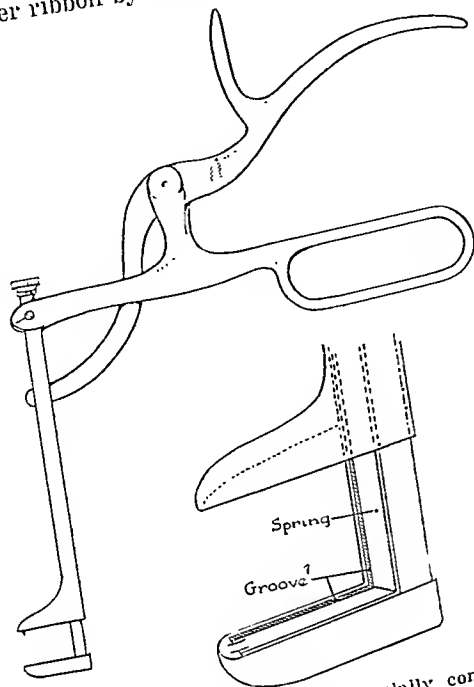


Fig. 3.—Drawing of the instrument showing especially constructed grooves in the jaws.

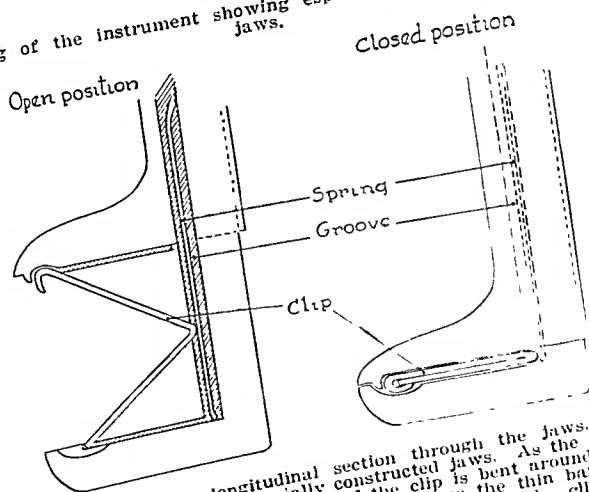


Fig. 4.—Drawing showing longitudinal section through the jaws. In the open position the clip is fitted into the especially constructed jaws. As the jaws are closed and the clip compressed, the projecting tip of the clip is bent around the lower end of the clip, automatically locking it. At the same time the thin bandlike spring is compressed backward to accommodate the greater length of the clip in the closed position.

# REFERENCE

1. DeBakey, Michael, Ochsner, Alton, and Schroeder, J.: Total Pneumonectomy in Dogs Using Auto-Locking Silver Clips. To be published.

nervous, endocrine, vascular, and unclassified. It is highly probable that time and increasing knowledge will prove this classification is also incomplete. It is quite possible that a renal arteriolar lesion which is incapable of being detected by our present diagnostic methods may be the underlying factor in many cases of nonrenal hypertension.

However, it should be emphasized that the exact etiologic relation between many of the disease entities and hypertension is not always clearly or definitely established, for in some instances there is reason to believe that their presence may be coincidental or at least controversial. In fact, some writers even venture to suggest that essential hypertension is not a clinical entity. McCann is of the opinion that in 80 to 85 per cent of the cases of essential hypertension the underlying condition depends upon atheromatous narrowing of the larger renal arteries at or near the aorta and that in 15 to 20 per cent the trouble is due to unsuspected lesions of the kidneys or of the urinary tract.

In the past two years the occurrence of various lesions in the urinary tract of patients suffering with hypertension has assumed greater etiologic significance, as attested by the statistical studies of Schroeder and Steele, Williams and Harrison, and Maher and Wosika and the numerous case reports of Boyd and Lewis, Leadbetter, Nesbit, Bothe, Braasch, Crabtree, and others.

#### INCIDENCE

It has been only in the past three years that attention has been directed to the occurrence of urologic disease in hypertensive patients. Wosika and Maher recently reviewed 600 cases of hypertension with especial reference to the causative or coincidental factors. They classified 70.97 per cent (425 cases) as essential hypertension or hypertension of unknown type. The remainder, 29.03 per cent (175 cases), were considered cases of secondary hypertension of which 16.5 per cent (99 cases) were examples of urologic hypertension and only 4.34 per cent (26) were cases of parenchymal renal disease; i.e., chronic nephritis, arteriosclerotic kidneys, etc. These authors subsequently published an analysis of the group of urologic hypertensive cases; i.e., 99 cases plus 2 cases of polycystic disease, a total of 101 cases, or 16.8 per cent, of a series of 600 cases. They observed that a single diagnosis seldom covered the entire urologic pathology and that the major urologic lesions were those of obstruction, infection, or a combination of both. The largest group was of the obstruction type, and the approximate levels of obstruction in 72 cases were found to be in the kidney pelvis (5), ureters (18), bladder inlet (9), bladder outlet (38), and unclassified (29). Prostatic disease accounted for 31 cases, or 53 per cent, of the male patients with hypertension. The next largest group contained 27 cases of chronic pyelonephritis and complications in which obvious obstruction was not readily demonstrated. Renal calculi occurred in

# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## HYPERTENSION AND UNILATERAL RENAL DISEASE

REVIEW OF THE LITERATURE AND REPORT OF 16 CASES

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### INTRODUCTION

IN THE past few years the fundamental conception of a nephritic and a nonnephritic ("essential") type of hypertension as advanced by Fishberg has undergone some modification, tending toward subdividing this concept into more specific entities. This change may be attributed to (a) many reports of hypertension associated with different types of renal and adrenal diseases and (b) the epochal contribution of Goldblatt on the experimental production of hypertension by constriction of the renal arteries by clamps and the renewed interest in the researches of other investigators.

It is my intention to review briefly some of the important clinical and experimental contributions to the subject of hypertension of the nonnephritic type and to report several cases of hypertension caused by unilateral renal disease which were cured or relieved by surgical treatment. Particular attention and emphasis will be paid to the relation of hypertension to diseases of the genitourinary tract. Individuals interested in the historical background of essential and urologic hypertension are referred to the excellent contributions of Fishberg, Weiss and Parker, Mulholland, Maher and Wosika, McCann, and others.

### CLASSIFICATION

A classification of hypertension is extremely difficult due to the complexity of its etiology and pathology and to the rapidly increasing knowledge concerning a variety of clinical diseases which cause hypertension and which were formerly classified under the diagnosis of essential hypertension. Consequently the classical conception of a nephritic and a nonnephritic (essential) hypertension appears to be inadequate. A more comprehensive classification of hypertension has been offered by Sehroeder and Steele which is based upon the clinical conditions associated with hypertension and is subdivided into five groups; viz., renal,

relative incidence of hypertension in association with unilateral renal lesions is presented and frequent reference to their findings is made elsewhere in this paper.

Crabtree and Chaset have recently attempted to evaluate the hypertensive tendency in 150 consecutive nephrectomies for severe unilateral renal damage. In this series only 14 cases (9.3 per cent) showed pre-operative hypertension; viz., chronic pyelonephritis, 7 cases; hypernephroma, 6 cases; and tuberculous pyelonephritis, 1 case.

#### EXPERIMENTAL HYPERTENSION

Before undertaking a discussion of the clinical relationship of non-nephritic renal lesions to hypertension, it seems appropriate to review and evaluate the experimental studies on the renal factor in hypertension.

The medical profession is greatly indebted to Goldblatt and his associates for their outstanding contribution in the field of experimental hypertension and for the interest in the clinical aspects of hypertension which their work created and stimulated. Their experiments were performed on dogs and their results have received universal recognition. Utilizing a specially devised clamp, they were successful in producing a persistent hypertension by two methods: (a) partial constriction of both renal arteries and (b) constriction of the renal artery of one kidney followed by the removal of the opposite kidney. A transient hypertension was produced when the renal artery of only one kidney was constricted and the other kidney was left intact. Wilson and Byrom subsequently showed that the latter procedure in rats resulted in a permanent hypertension with all its consequent changes. Goldblatt and his associates demonstrated that the resultant hypertension varied directly with the degree of ischemia induced by constriction of the renal arteries; viz., moderate constriction of the renal arteries resulted in a definite, but not extreme, hypertension which corresponded to that of benign hypertension in man; whereas, severe constriction of the renal arteries led to an early but marked hypertension which was soon followed by renal insufficiency and the picture was comparable to the malignant hypertension in man. Following severe constriction of the renal arteries, small and large hemorrhages and hyalinized and necrotic arterioles were observed in the various organs, except in the constricted kidney which was considered to be "protected" by the renal ischemia.

Following the epochal contribution of Goldblatt there has been a revival of interest and investigation concerning the etiology and renal factor in hypertension. A comprehensive search of the literature has revealed an abundance of experimental studies on this subject which unfortunately has been forgotten or overlooked or whose significance has not been fully appreciated.

Animal experimentation has demonstrated that an increase in arterial tension can be produced by a variety of procedures whose purpose is

17.8 per cent. As a result of this study they concluded that hypertension appears to be associated with urologic pathology more frequently than is ordinarily believed.

Schroeder and Steele studied 218 cases of hypertension and in the renal group of 58 cases, there were 14 cases of glomerulonephritis, 8 calculi, and 4 pyelonephritis. In 29 cases there were factors of stone, infection or obstruction alone, or in combination. In another study the same authors reviewed 71 cases of essential hypertension in young subjects who revealed no renal functional impairment as determined by the ability of the kidneys to concentrate urine and by the standard urea clearance test. Abnormalities of the kidneys and ureters were revealed by intravenous urography in 50 of 71 cases. More than one-half of the patients had some form of urinary obstruction. Harrison and Williams presented a similar study with comparable results. In a series of 100 cases previously diagnosed as essential hypertension, evidence of urinary tract disease was found in 30 patients. In most cases the urologic disease apparently antedated the onset of hypertension; viz., 6 patients gave a previous history of kidney colic, 10 had experienced acute pyelitis, and 3 had unexplained hematuria. Subjective symptoms of vesical irritability and pain in the kidney region were noted in 17 of 30 patients, evidence of urinary obstruction was present in 8 patients, and urinary tract infection was found in 5 patients but was associated with some other factor which may have played a role in causing the hypertension.

Oppenheimer, Klemperer, and Moschkowitz have made noteworthy contributions to the incidence and relation of unilateral renal disease to hypertension. They reviewed 5,000 consecutive autopsies and found the incidence of hypertension in the whole group to be 24 per cent, as compared to 40 per cent in the group of 97 cases with unilateral renal disease. Further analysis of the latter group revealed hypertension to be present in 15 (83 per cent) of 18 cases of unilateral narrowing of the main renal artery, in 21 (32 per cent) of 66 cases of unilateral hydronephrosis and chronic pyelonephritis, and in 3 (23 per cent) of 13 cases of unilateral congenital hypoplasia.

Chute recently reviewed 353 cases of essential hypertension and found 42 cases (12 per cent) with renal lesions; 22 had demonstrable pathology and 20 gave a history of pyelitis or the passage of calculi but did not have complete urinary studies.

Braasch, Walters, and Hammer recently made an important and comprehensive study of the incidence of hypertension in a group of 1,684 patients subjected to renal surgical operation. In this group approximately the same percentage (315 patients, or 18.7 per cent) had preoperative hypertension as that observed in a series of 975 consecutive adult patients taken at random; namely, 195 cases of hypertension, or 20 per cent. In their article a detailed analysis of the

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Animal experimentation has demonstrated that an increase in arterial tension can be produced by a variety of procedures whose purpose is

to decrease the blood flow through the kidney. This has been accomplished by: (1) removal of large portions of the total kidney substance (Passler and Heineke, Cash, and Chanutin and Ferris); (2) partial ligation of renal arteries (Janeway, Hartwick, Freidman, Collins and Drury); (3) constriction of renal veins (Bell and Pederson and Mendenez); (4) constriction of blood supply by cellophane perinephritis (Page); (5) production of interstitial fibrosis of kidneys by exposure to x-ray (Hartman, Ballinger, and Doub); (6) compression of renal arteries with adjustable clamps (Goldblatt, Lynch, Hanzal, and Summerville and Wilson and Bryom); (7) constriction of blood supply of solitary kidney transplanted to neck (Blalock and Levy); (8) constriction of blood supply of solitary kidney transplanted to groin (Glenn, Child, and Heuer); (9) ligation of one or both ureters (Rautenberg, Hartwick, Harrison, Mason, Resnik, and Rainey, Williams, Wegria, and Harrison, and Blalock and Levy).

Since each of the above procedures causes a decrease in the volume of blood passing through the kidney and is followed by a systemic rise in blood pressure, it has been assumed by many investigators that renal ischemia is the primary or initiating factor in the production of the hypertension. The evidence offered in support of this theory is based chiefly upon deficiency of renal tissue and impairment of renal circulation as accomplished by reducing the total kidney volume by multiple operations (Passler and Heineke), by removing 80 to 85 per cent of the total kidney substance (Cash), or by removing five-sixths of the total kidney substance (Chanutin and Ferris). Further evidence is found in the work of Blalock and Levy, who demonstrated conclusively that the renal blood flow was decreased in dogs with hypertension caused by constricting the renal artery with Goldblatt's clamp.

Drury has described a method for the production of renal insufficiency and atrophy of any grade in rabbits without the production of pathologic changes in the renal epithelium. He employed a loose silk ligature on the left renal artery of baby rabbits to act as a check on renal growth. The diameter of the loop was regulated by tying silk down on wire of known diameter and withdrawing the wire. By this method dwarfed kidneys, varying from 20 per cent to 45 per cent of the total normal combined kidney weight, were obtained and a compensatory hypertrophy occurred in the opposite kidney. He found that a relatively high degree of hypertension develops in renal atrophy before the removal of the compensatory hypertrophied kidney. Following removal of the hypertrophied kidney, the hypertension increased. Secondary changes resulting from renal atrophy included loss of appetite and weight, anemia, disturbance of equilibrium, hemorrhages in the intestinal wall and eyeball, and cardiac hypertrophy.

Recently Jeffers and his associates were able to produce experimental hypertension in nephrectomized parabiotic rats. They found that parabiotic rats survive the removal of both kidneys of one parabiont,

and that following the removal of a third kidney from the other parabiont, the majority of the animals developed hypertension.

However, there is some evidence available to show that renal ischemia is not the only factor concerned in the mechanism of hypertension. Bilateral nephrectomy does not cause an elevation of blood pressure, as shown in experiments of Cash, Hartwick, and Harrison, Mason, Resnik and Rainey. Similar results were obtained following the bilateral ligation of all renal vessels plus bilateral ligation of the ureters by Cash and Blalock and Levy. Goldblatt recently pointed out that the production of hypertension through ischemia appears to depend on the patency of the ureter. He observed that constricting the main renal artery of one kidney causes a systemic rise in blood pressure, but if the ureter of the ischemic kidney is occluded at the same time, no rise in blood pressure occurs. Furthermore the studies of Dock and Rytand on rats with hypertension due to progressive extirpation of renal tissue demonstrated that the blood flow per gram of tissue is as great in such animals as in normal control. Katz, Friedman, Rodbard, and Weinstein found that the severity and persistence of the effect of renal ischemia are dependent upon the ratio of ischemia to normal renal tissue.

The exact mechanism or agents responsible for the elevation of the blood pressure has not been definitely established. Some investigators attribute the increase in arterial tension to a reflex effect from the ischemic kidney; others maintain that this phenomenon is due to the production of a pressor substance in the ischemic kidney. Various experimental evidence has been gathered which tends to refute the "reflex" theory, or, at least, demonstrates that the hypertension associated with an ischemic kidney of the Goldblatt type cannot be prevented or relieved by the following procedures; viz., (1) denervation of the kidney pedicle (Page, Freeman and Page); (2) excision of the splanchnic nerves (Goldblatt and co-workers); (3) complete sympathectomy (Alpert, Alving, and Grimson); and (4) complete destruction of the spinal cord (Glenn, Child, and Page).

The only evidence in favor of a central action of the pressor substance in renal hypertension is found in the work of Dock and Rytand, who showed that the blood pressure of rats with renal hypertension fell to the same level after section of the spinal cord as did the blood pressure of normal rats.

There appears to be ample evidence in support of the formation of a chemical substance in either the ischemic kidney or the unaffected kidney which possesses a pressor effect on the vasoconstrictor nerves or directly upon the blood vessels. As early as 1898 Tigerstedt and Bergman demonstrated the presence of a pressor substance in the saline extracts of normal rabbit kidneys, which they designated as renin. They found that this extract caused an increase in blood pressure when injected intravenously in anesthetized dogs. Fasciolo, Houssay, and Taquini demonstrated the presence of a pressor substance in the blood

of the renal vein of a Goldblatt type of kidney by testing for its vasoconstrictor effects on a toad. However, Boylston, McEwen, and Ivy were unsuccessful in their attempts to demonstrate this substance in the perfusate of ischemic kidneys with Loeke's solution. Prinzmetal, Friedman, and Abramson found that saline extracts of ischemic kidneys of dogs and of kidneys of patients dying with benign and malignant hypertension, chronic nephritis, and chronic pyelonephritis yielded greater pressor effects than similar extracts of normal human kidneys. Friedman and Prinzmetal observed that the blood of patients with hypertension exhibited no pressor effect when transfused into patients with normal blood pressure. Katz, Friedman, Rodbard, and Weinstein transferred small amounts of blood from a hypertensive to a normal dog without producing a rise in blood pressure. Solandt, Nassin, and Cowan observed that blood from a dog with a Goldblatt type of kidney produced a transient hypertension in another dog, provided the recipient animal was deprived of both kidneys. Taquini found that acute complete ischemia of the kidney produces a pressor substance as does the partially ischemic (Goldblatt type) kidney.

The physiology and pharmacology of renin have been intensively studied, but the investigators are not in complete accord in their findings. Tigerstedt, Williams, Harrison, and Mason, and Helmer and Page considered renin to be a protein; whereas, Atumi believed it to be a sterol. Tigerstedt, Page, and Merrill, Williams, and Harrison maintained that the pressor effect of renin was elicited by direct action on the blood vessels. The latter investigators have shown that its action is not influenced by elimination of the nervous system, pituitary, adrenals, pancreas, liver, or kidneys. Fasciolo, Houssay, and Taquini showed that the presence of a healthy kidney is capable of diminishing its pressor effects. Tigerstedt and Page observed that successive injections of renin resulted in diminishing pressor responses.

Merrill, Williams, and Harrison studied the effect on the intrinsic circulation of two pressor substances isolated from the kidney; viz., renin, obtained from saline extracts, and a tyrosine-like substance from the autolysate. The former was found to elevate the blood pressure, increase the size of the kidney, increase the blood flow through the kidney, and increase the volume of urine, and its effect was believed to be due to constriction of the efferent arterioles of the glomeruli. These findings were substantiated by Coreoran and Page. The latter substance caused a shrinkage in the volume of the kidney and a diminution of renal blood flow as a result of the constriction of the efferent arterioles. Landis, Montgomery, and Sparkman observed that when the toxic and depressor fractions are removed from the crude saline extracts of kidney tissue, the remaining solution elevates the blood pressure without reducing peripheral flow. The Chesleys studied the renal blood flow by means of the diodrast clearance test in 37 women having hyper-

tension and renal impairment occurring separately and together. They found that hypertension sometimes occurs with a normal blood flow and that a marked diminution in renal blood flow may be found in patients with a normal blood pressure. They observed that the urea clearance often parallels the renal blood flow. In the majority of patients having hypertension, the renal blood flow is considerably reduced below average.

Recently Harrison, Grollman, and Williams were successful in extracting from normal kidneys a "renal antipressor substance" which was shown to have no effect upon the blood pressure of normal animals but appeared to possess the property of neutralizing the effects of renin, ephedrine, and other pressor substances. The important significance of these findings is that they offer an explanation of the absence of hypertension in those unilateral renal diseases which one would expect to develop hypertension; viz., the amount of antipressor substance elaborated by the healthy kidney overbalances or offsets the effect of the pressor substance produced by the diseased kidney.

As indicated before, an increase in blood pressure has been produced experimentally by ligation of one or both ureters by Rautenberg and others. Williams, Wegria, and Harrison found that in rats unilateral ligation of the ureter did not always cause hypertension but bilateral ligation always resulted in hypertension, and that the pressor response to renin was more marked in bilateral cases. Blalock and Levy noted that hypertension induced by unilateral ligation of the ureter was abolished by the removal of the affected hydronephrotic kidney. This is in accord with the observation of Goldblatt that the excision of the ischemic kidney, resulting from constriction of one renal artery with a clamp at the height of hypertension, is followed by a prompt return of the blood pressure to a normal level.

Various investigators have reported secondary pathologic phenomena in experimental hypertension which bear a close relationship to the changes observed in clinical cases of hypertension. For example, Gibson and Robinson observed cardiac hypertrophy in dogs with hypertension caused by constriction of the renal artery by a Goldblatt clamp; no constant changes in the blood volume were noted and no impairment in renal function was found. Chanutin and Barksdale observed left ventricular hypertrophy and hypertension in rats following partial nephrectomy. Wilson and Pickering demonstrated acute arteriolar lesions of the malignant variety in rabbits with hypertension resulting from constriction of renal artery with Goldblatt's clamp. They were of the opinion that the incidence of these lesions was related to the degree of hypertension rather than to its duration. Similar changes were found in the arterioles of the intestines, liver, adrenals, eyes, and heart. The arteriolar changes were not found in the ischemic kidney but rather in the contralateral and presumably normal kidney. These changes in the intrinsic circulation of the rabbit differ from those found in human

beings with malignant hypertension. Winternitz and Waters observed gross vascular lesions involving the pulmonary artery, aortic arch and its branches, thoracic aorta, superior and inferior vena cava, and the myocardium, as well as visceral hemorrhages following constriction of the renal artery. The mural changes in the blood vessels were similar to the vascular lesions of malignant nephrosclerosis in man. Wood and Ethridge were able to produce hypertension with arteriolar and glomerular changes in the albino rat by subtotal nephrectomy.

From this mass of interesting, but at times conflicting, experimental data one may safely conclude that a specific type of hypertension may be of renal origin. One of the primary etiologic factors in this type of hypertension is renal ischemia which can be produced in the affected kidney. The exact manner in which this substance exerts its effect on the blood pressure has not been definitely established. Munoz, Braun-Menendez, Fasciolo, and Leloir offered the following explanation of the mechanism of renal hypertension: "Renal ischemia determines the secretion of 'renin.' This protein is an enzyme which acts on a blood globulin ('hypertensin precursor') and gives rise to a substance ('hypertensin') which produces vasoconstriction. Another enzyme, 'hypertensinase,' which destroys 'hypertensin' is present in the blood and tissues." Kohlstaedt and Page recently proposed what appears to be the first definite theory to explain the physiologic mechanism of experimental renal hypertension. They perfused the isolated normal canine kidney with defibrinated blood under varying hemodynamic conditions, and by subsequent pulsate perfusion through the isolated rabbit's ear, studied the pressor effects of venous blood samples which were activated with renin complement ("hypertensin precursor") to form angiotonin ("hypertensin"). They found that the excised normal canine kidney perfused under normal pulsate arterial pressure did not secrete renin into the venous blood, but when the renal artery was partially clamped for 100 or more minutes, the venous blood samples possessed vasoconstrictor properties. From these and other experiments they maintained that the essential factor responsible for the liberation of renin is not changes in blood pressure or perfusion rate but reduced pulsate pressure. On the basis of these experiments they formulated the following theory to explain the mechanism of experimental hypertension: Compression of the renal artery causes a partial conversion of pulsate to continuous blood flow in the kidney with resulting edema and anoxemia of the cells of the tubules. This is followed by an increase in cellular membrane permeability which allows the liberation of the large renin molecule. The liberated renin reacts within renin activator to produce angiotonin which in turn raises the blood pressure and produces constriction of the efferent glomerular arteriole with further tubular anoxemia. Thus a vicious cycle is set up which results in a sustained

arterial hypertension. This interesting and plausible theory requires further clinical and experimental research before it can be accepted.

Grollman, Williams, and Harrison recently reported on the chemical and pharmacologic properties of a renal antipressor substance. They found that when extracts containing the renal antipressor substance were administered orally to normal animals, they did not produce a decline in blood pressure but did have the property of partially inhibiting the pressor effect of subsequently injected renin. When extracts containing a sufficient amount of renal antipressor substances were administered either parenterally or orally to animals with experimental renal hypertension, a marked and prolonged decline in blood pressure occurred. The administration of the antipressor substance by similar routes to a small group of patients with hypertension resulted in a decline in blood pressure. However, the authors emphasized the fact that it is unwise to draw any conclusions from such a small series of cases and preferred to wait until a much larger series of cases is studied.

There is no positive evidence to show that the kidney is concerned in the production of all types of hypertension. These experimental observations are not only of theoretical interest but also of great practical importance, for they have established on a firm basis the renal origin of hypertension and should stimulate, and in many cases have stimulated, intensive clinical study of every case of hypertension particularly from a urologic standpoint.

#### CLASSIFICATION OF NONNEPHRITIC DISEASES OF THE KIDNEY ASSOCIATED WITH HYPERTENSION

The following is a classification of nonnephritic diseases of the kidney which cause or are accompanied by hypertension, and in many instances, are amenable to surgical treatment. The nephritides associated with hypertension are purposely omitted. The important etiologic factor in each lesion is renal ischemia resulting from interference with renal circulation by the disease process. This may be brought about by intrinsic factors operating within one or both kidneys or by extrinsic factors usually affecting the main arterial supply of one or both kidneys. No attempt has been made to classify the specific causative lesions from the standpoint of their unilaterality or bilaterality, as this phase of the subject is considered in the subsequent discussion of the role of each causative lesion.

- I. Inflammatory disease (acute and chronic)
    - A. Pyelonephritis
    - B. Tuberculosis
    - C. Infections complicating other lesions; i.e., calculi, hydronephrosis, polycystic disease, etc.
  - II. Obstructive lesions
    - A. Hydronephrosis
    - B. Pyonephrosis
    - C. Nephroptosis
- } Associated with obstructive, inflammatory or neoplastic lesion in the lower urinary tract or genital tract

### III. Vascular lesions

- A. Arteriosclerotic kidney
- B. Localized arteriosclerosis of renal arteries
- C. Arteriolosclerosis of kidney
- D. Thrombosis of large and small renal arteries with or without infarction
- E. Infarct of kidney
- F. Spasm of renal vessels
- G. Inflammatory or obliterative lesions of renal arteries and arterioles
  - 1. Endarteritis; i.e., obliterans type
  - 2. Thromboangiitis obliterans
  - 3. Periarteritis nodosa
- H. Traumatic injuries of kidney, parenchyma, and vascular pedicle
- I. Compression of renal vessels by intrinsic or extrinsic lesions; i.e., tumors, aneurysms
- J. Miscellaneous lesions
  - 1. Thrombosis of abdominal aorta
  - 2. Coarctation of aorta
  - 3. Aneurysm of aorta, etc.
- IV. Neoplasms of kidney and adrenals
  - A. Kidney tumors in adults
  - B. Kidney tumors in infants and children
  - C. Adrenal tumors
- V. Congenital renal anomalies
  - A. Anomalies of kidney; i.e., form, structure, position, etc.
  - B. Anomalies of blood vessels; i.e., course, position, size, and lumen
  - C. Congenital cystic disease; i.e., polycystic disease

**I. INFLAMMATORY LESIONS OF KIDNEY ASSOCIATED WITH HYPERTENSION.**—Prior to 1930 hypertension of renal origin was regarded as a relatively rare disease and was usually considered as limited to acute and chronic glomerulonephritis and a few other uncommon diseases of the kidney; i.e., polycystic diseases, nephrosclerosis, etc. However, since that time the prevailing concept that the vast majority of hypertension cases were of the essential (nonrenal) type has undergone a gradual but decided revision in the minds of most clinicians and even has been completely discarded by a few clinicians.

**A. Pyelonephritis.**—Of all the inflammatory diseases bearing some relation to hypertension, chronic pyelonephritis appears to be the one disease toward which most attention has been directed in recent years. Before attempting a discussion of the association or relation of hypertension to chronic pyelonephritis, it is important to have an accurate and clear conception of this pathologic entity inasmuch as considerable confusion and misunderstanding prevail in the literature regarding the exact definition and description of chronic pyelonephritis. This is evidenced by the numerous conflicting definitions which have been used, heretofore, synonymously and, too often, incorrectly; i.e., renal agenesis, aplasia, hypoplasia, or atrophy; atrophic pyelonephritis, nephrofibrosis, nephrosclerosis, etc.

One of the chief points of contention has been the exact pathologic significance and clinical interpretation of the various types of renal

atrophy. The need for a more descriptive and inclusive term than renal atrophy is quite obvious when one realizes that atrophy merely suggests a reduction in size of the organ and fails to take into consideration the etiology. Further, it is essential that one recognize the true nature of the atrophic kidney from the standpoint of its effect upon renal function, its relation to infection or obstruction in the urinary tract, its relation to hypertension before instituting a rational plan of treatment, surgical or otherwise, not only of the renal lesion, but also of the underlying factors or lesions in the urinary tract which may be responsible for its production.

Several writers have attempted to clarify and define the various types of renal atrophy. In the main, they have classified the cases into two main groups: (a) congenital atrophy, which is the result of a developmental defect in the metanephric mass; i.e., renal agenesis, aplasia, and hypoplasia; and (b) acquired atrophy, due to a disease process. Cumming and Schroeder employed the term nephrofibrosis for the latter group, which they defined as a "localized or diffuse destructive or degenerative condition of the kidney which may or may not have originated as an infective or infected embolic process but results in a decrease in the size of the organ due to fibroplastic proliferation." They classified the etiologic factors of "nephrofibrosis" as follows: (1) obstruction, (2) trauma, (3) postoperative, (4) infection, (5) calculosis, (6) idiopathic (atrophy of disuse). They distinguish nephrofibrosis from nephrosclerosis, the latter being considered as a degenerative vascular change in the kidneys associated with generalized vascular disease and having an entirely different etiology and symptomatology. I personally agree with this classification and definition but prefer the term chronic atrophic pyelonephritis as more descriptive and inclusive than nephrofibrosis.

As early as 1910, Longcope and McClintock mentioned the clinical relationship between chronic pyelonephritis and hypertension. Following this important contribution, interest appeared to lag, as evidenced by the fact that in 1930 Bell and Pedersen discussed the causes of hypertension and noted that there had been no reports of hypertension caused by pyelonephritis. However, interest has been revived in recent years, as attested by the studies and reviews published by Longcope, Butler, Crabtree, Weiss and Parker, McCann, Putschar, Kimmelstiel and Wilson, Braasch, and others. It is from their excellent contributions that much of the following information has been drawn.

In 1932 Staemmler collected 30 cases of pyelonephritis with contracted kidneys, marked elevation of blood pressure, and cardiac hypertrophy. In 1933 Longcope and Winkenwerder described 9 patients with supposed chronic nephritis with uremia, who at autopsy had a bilateral pyelonephritis, contracted kidneys, and irregularly dilated pelvises. Although hypertension was present in 5 cases, the authors failed to emphasize chronic pyelonephritis as the cause of the hypertension.

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Putschar has studied the histogenesis and morphologic findings in acute and chronic pyelonephritis. He pointed out that a chronic progressive type of pyelonephritis is not uncommon and that in the majority of such cases purulent exudate and abscess formation may be entirely absent. He maintained that the inflammation creeps along in the interstitial tissue and causes progressive fibrosis and scarring in the kidney areas. This process may be restricted to one portion of the parenchyma or involve the entire kidney; it may be unilateral or bilateral. Pyelonephritic contracted kidneys are observed more commonly in women than in men (3:1). In cases of unilateral contracted kidney, a marked compensatory hyperplasia occurs on the opposite side. Kimmelstiel and Wilson have described two types of glomerular lesion in chronic pyelonephritis. The first type, which is peculiar to this condition, is due to the extension of the interstitial inflammation to the glomeruli. The second is an "alterative" type of glomerulitis which occurs in the pyelonephritic contracted kidney as a manifestation of a generalized vascular disease. The latter type is independent of the former but is practically indistinguishable from the focal glomerulitis found in so-called essential hypertension of the benign or malignant type.

Peters and his associates have shown that not infrequently pregnancy may precipitate the hypertensive phase of pyelonephritis which, in turn, may initiate the eclamptic syndrome. Crabtree and Prien maintained that hypertension is not the ruler in severely injured kidneys due to pregnancy pyelonephritis, as they found hypertension in only 2 of 30 cases of severe bilateral pyelonephritis in pregnancy at from ten to eighteen years after initial injury. They considered that infectious injuries to the arteries of the cortex served as possible cause for setting in motion the requisite forces responsible for hypertension in these cases. They also emphasize the fact that in bilateral cortical necrosis of kidney, a frequent complication of pregnancy, a rise in blood pressure is seldom observed despite the fact that the patients excrete little or no urine for long periods of time, varying from six to twenty-five days.

In a subsequent five- to ten-year follow-up study of 45 patients with pyelonephritis of pregnancy, Crabtree and Reid noted that the prognosis was grave for patients with both toxemic and pyelonephritic injury as indicated by the fact that all 3 patients with both conditions had hypertension and 2 of these were dead five years after the injury. Elevations in blood pressure above 150/90 with evidence of renal insufficiency were found in 6 patients with pyelonephritis of pregnancy. Renal calculi were found in 5 patients. They maintained that pyelonephritis of pregnancy was a progressive disease in many cases. In a review of the previous two series of cases Crabtree concluded that a high percentage of pregnancy pyelonephritic cases show evidences of renal damage after five to eighteen years and that hypertension is not the rule in the same group of cases, as only 8 of 72 cases developed hypertension.

In 1936 Kimmelstiel and Wilson studied the incidence of hypertension and renal insufficiency in 56 cases of pyelonephritis. Primary lesions in the genitourinary tract were present in 29 of these cases. They classified their cases in four groups: (1) acute focal nephritis (neither hypertension nor renal insufficiency); (2) acute diffuse pyelonephritis (13 cases; 9 died in uremia; hypertension in 4 cases); (3) chronic diffuse pyelonephritis (with focal or unilateral contraction of kidney; hypertension present in 6 of 9 cases; uremia cause of death in 3 hypertensive patients); (4) chronic diffuse pyelonephritis (26 cases; hypertension and uremia associated in 16; hypertension alone in 4; uremia alone in 6).

In 1937 Longcope reported the results of a continuous study of 22 cases of chronic pyelonephritis which terminated fatally. He observed that hypertension occurred in 50 per cent of the cases and was a late or terminal feature of the disease. He maintained that the hypertension could not be ascribed to a diminution of renal functional capacity inasmuch as several patients died of renal insufficiency without hypertension. He did not emphasize the vascular lesions of pyelonephritis or their relation to hypertension.

Weiss and Parker made an excellent and comprehensive clinicopathologic study of 100 cases of chronic pyelonephritis, and their findings confirm the clinical observations of Longcope. They have emphasized certain pathologic features of pyelonephritis whose morphologic and clinical significance has not been well recognized or fully appreciated. A summary of their most pertinent findings are herewith presented:

- a. The structural characteristics of pyelonephritis are essentially the same regardless of the type of infection; i.e., hematogenous, urogenous, or lymphatic.
- b. Pathologic changes involve the renal lymphatic and vascular systems as well as the nephron and interstitial tissue.
- c. Pyelonephritis, particularly in the chronic and healed stages, is frequently associated with hypertension, and pyelonephritis is the causative lesion in at least 15 to 20 per cent of malignant hypertensive cases.
- d. There is a relation between the severity and diffuseness of the vascular lesions of pyelonephritis and the arterial hypertension. Cases of severe hypertension showed changes characteristic of advanced hyperplastic arteriosclerosis, productive endarteritis, and necrotizing arteriolitis which are similar to those observed in malignant nephrosclerosis. The vascular changes and the renal functional damage are due to the same cause, but may be independent of each other.
- e. The vascular changes of chronic pyelonephritis are restricted to the kidneys in contrast to the generalized changes observed in malignant hypertension.
- f. Chronic or healed pyelonephritis rarely coexists with chronic glomerulonephritis; the former condition is more frequent than the latter.
- g. Pyelonephritis may complicate polycystic disease, hydronephrosis, and tuberculosis. However, the vascular lesions characteristic of chronic pyelonephritis do not occur in tuberculosis or hydronephrosis uncomplicated by pyelonephritis.

nephritic contracted kidney following chronic pyelitis of childhood; no improvement occurred in the patient in Case 2, who had a contracted pyelonephritic kidney as a result of pyelonephritis of infancy and pregnancy and died of renal failure five months after nephrectomy; no improvement was noted in the patient in Case 4, who had arterial hypertension of nine years' duration and whose right kidney was removed for advanced pyelonephritic contraction and ptosis. In the last 3 cases advanced arteriolar sclerosis was present in the kidneys.

Everett reviewed the findings in forty-one consecutive nephrectomies and found extensive chronic pyelonephritis with severe vascular lesions in the smaller arteries and arterioles in 19 patients. In the latter group 6 patients had suffered from hypertension and only 3 had a reduction in blood pressure following nephrectomy. Walters and Barker reported 5 cases of unilateral chronic atrophic pyelonephritis associated with hypertension which were successfully treated by nephrectomy. In each case the blood pressure returned to normal limits following the operation. In each case pathologic studies of the diseased kidney showed extensive atrophy and scarring with marked thickening of the arterial walls in the scarred areas. In a series of 57 cases in which a diagnosis of chronic atrophic pyelonephritis was made urographically, an elevation of the blood pressure (i.e., in excess of 145 mm. systolic and 90 mm. diastolic) was noted in 26 cases (45.6 per cent). In a series of 24 cases in which the diagnosis was made from pathologic studies following nephrectomy, 15 cases (62.5 per cent) showed elevations in blood pressure.

Braasch observed 47 cases of hypertension in 180 cases of chronic pyelonephritis. Hypertension occurred more frequently in patients with marked pyelographic changes and in those with impaired renal function. Hypertension was found in 26 per cent of the patients with chronic pyelonephritis as compared with 20 per cent of controls in the same age group. He maintained that pyelonephritis served as an irritant to bring out a latent hypertension. He stated that pyelonephritis does not produce hypertension in an otherwise normal person.

Braasch, Walters, and Hammer reported preoperative hypertension in 20 of 43 patients treated by nephrectomy for primary atrophic pyelonephritis, an incidence of 46.5 per cent. The incidence of hypertension was decidedly lower in patients who had nephrectomy for pyelonephritis without atrophy or sclerosis. They studied the postoperative course of the blood pressure in 18 of 43 operative cases of atrophic pyelonephritis. They found that preoperative hypertension was present in 10 of these 18 patients and that following operation the blood pressure returned to normal in 7 patients and was not influenced in 3 patients. Of the 8 patients who had a normal blood pressure preoperatively, hypertension developed after operation in only 1 case. They observed that the percentage of cases in which blood pressure was permanently reduced after nephrectomy for atrophic pyelonephritis was far greater

Weiss, Parker, and Robb maintained that the infection in pyelonephritis may heal but that the hypertension initiated by the inflammatory changes may continue to progress. While it is generally recognized that hypertension may develop before any evidence of renal insufficiency presents itself in cases of chronic pyelonephritis, the exact mechanism responsible for the increase in arterial blood pressure has not been clearly established. Weiss and Parker offered the following interesting explanation for the pathogenesis of hypertension in these cases; viz., (1) the chronic progressive inflammatory processes caused vascular changes within the kidney with resulting ischemia; (2) the renal ischemia tended to initiate the hypertension; (3) the hypertension in turn accentuated proliferative vascular changes by altering the permeability of the walls of the renal blood vessels; (4) the alteration of the permeability permitted certain substances to exude into the perivascular tissues which, in turn, aggravated proliferative processes in the blood vessels, thereby increasing the ischemia. Thus a vicious circle is set up.

Some writers have raised the objection that the hypertension is not always related to the chronic pyelonephritis in the above type of case but rather is the result of other causes or lesions which occur in the latter period of life and are not always discernible. However, such objections and claims are invalidated by the frequent reports of hypertension in infants and young adults with chronic pyelonephritis. In 1937 Butler emphasized the definite relation between chronic pyelonephritis and arterial hypertension in children. In a series of 15 cases of pyelonephritis in children, he observed hypertension in 8 cases and reported 2 cases of chronic unilateral pyelonephritis with hypertension in children whose blood pressure returned to normal after nephrectomy. The latter are the first recorded cases to substantiate the contentions that sustained hypertension in human beings may be due to chronic inflammatory disease of one kidney and that removal of the affected kidney results in cure. One of these cases was subsequently reported by Barney and Suby. Bothe and Patch and associates obtained good results in similar cases in young children treated by nephrectomy. Cases of unilateral chronic pyelonephritis with hypertension in adults, which have successfully been treated by nephrectomy, have been reported by Crabtree, Barney and Suby, Walters and Barker, Neshit and Ratliff, Bothe, McIntyre, Schroeder and Fish, and Everett.

Schroeder and Fish reported 4 cases of arterial hypertension due to chronic pyelonephritis and treated by nephrectomy. Varying degrees of arterial and arteriolar changes were present in all kidneys removed in addition to the chronic inflammatory changes. The results varied; a marked improvement was noted in the patient in Case 7, who had a hypoplastic kidney with slight inflammatory and vascular changes; a slight improvement manifested by a temporary fall in blood pressure was obtained in the patient in Case 5, who had a unilateral pyelo-

pyelonephritis. There were moderately advanced sclerotic changes in the walls of the smaller vessels in the kidney and adrenal which were graded 2+.

CASE 2.—(G. U., No. 103221.) I. W. M., 50 years of age, male, white, married, high-school teacher, was referred to me for urologic study after admission to the Sinai Hospital on July 30, 1939, complaining of severe headaches. Both parents had died of "cerebral apoplexy" and one brother died at the age of forty-seven years of chronic nephritis. The patient had enjoyed good health until five months previously, when he developed severe occipital headaches accompanied by nausea and occasionally blurred vision. His condition became progressively worse with a gradual loss of strength and appetite and increased fatigability. For the past twenty years he has been troubled with diurnal frequency (every one to three hours) and pollakiuria, but no urgency, nocturia, dysuria, gross hematuria, retention, renal colic, or pain, etc. About fifteen months before he was examined for insurance and was told that his urine was negative and that his blood pressure was 150/100. On admission to the hospital blood pressure was taken daily and varied between 220 and 228 systolic and 116 and 124 diastolic. Ophthalmoscopic examination disclosed a marked tortuosity of the vessels with decided A-V nicking and many old hemorrhagic areas.

Physical examination was essentially negative except for the usual signs of cardiac hypertrophy and slight tenderness. The prostate was the seat of a mild chronic infection. The urine showed a specific gravity of 1.016, a faint trace of albumin, and on microscopic examination contained an occasional red blood cell and pus cell, and hyaline and granular casts. Blood studies revealed no anemia or leucocytosis. A combined phthalein test yielded a total of 38 per cent for two hours with the following successive half-hour estimations: 22, 10, 6, 0 per cent. Blood chemistry studies revealed the blood urea to vary between 78.09 and 97.07 mg. per cent; the blood chlorides between 412 to 433 mg. per cent; the  $\text{CO}_2$  combining power between 36.5 and 56; uric acid, 3.8 mg. per cent, total protein, 6.98 mg. per cent. Urea clearance and concentration tests, which were done prior to hospitalization, showed impairment of renal function. A diagnosis of malignant hypertension was made, and the patient was referred for urologic study.

Intravenous urography revealed a normal kidney and calyces on the right but evidences of compression and distortion of the infundibular portions of the upper and middle major calyx on the left and incomplete filling of the terminal portions of these calyces. On the basis of these pyelographic changes, a presumptive diagnosis of (1) chronic pyelonephritis with cystic degeneration, (2) chronic nephritis with cortical cysts, or (3) solitary renal cyst or tumor was made and retrograde pyelography advised. The latter was done and compression changes involving the renal pelvis and upper and middle major calyces were found which were more suggestive of a solitary cyst than a neoplasm.

After lengthy discussion with the patient and his family physician, in which the dangers of operation were stressed and no hopes or promises of a cure were given, an exploratory operation through a left lumbar incision was performed on Aug. 1, 1939, under avertin-ether anesthesia. A large, round solitary cyst, measuring 8 cm. in diameter, was found on the posterior aspect of the kidney extending down to, but not invading, the pelvis. A resolving cortical abscess 1 cm. in diameter was present on the convex border near the lower pole of the kidney. An aberrant vessel entering the anteromedial aspect of the upper pole of the kidney was present. The main artery appeared to be slightly thicker than normal. It was impossible to remove the cyst without doing irreparable damage to the kidney. After much deliberation and consultation with the family physician, a left nephrectomy was done. Convalescence was complicated by a rather severe episode of hiccoughs occurring

than when nephrectomy was performed for any other type of renal lesion. They maintained that the widespread atrophy of the renal tissues and the sclerosis of the renal blood vessels were responsible for the hypertension. They noted that acute cortical renal infection or perinephritic abscess was seldom a factor in causing hypertension.

In their series of 7 cases of chronic pyelonephritis with hypertension treated by nephrectomy, Crabtree and Chasot observed a slight improvement in blood pressure in only 1 case.

CASE 1.—(G. U., No. 1284.) J. P., 52 years of age, white, male, married, grocer, was referred for a urologic study on June 1, 1932. He had been treated for "stomach trouble" for the past ten years. He had had cramplike pains in the lower left quadrant lasting from five to six hours and recurring at intervals of from three to four months. The pain was accompanied by nausea and vomiting, particularly after eating. There was a moderate amount of epigastric discomfort, belching, eructation, and heartburn. The patient gave a history of diurnal frequency every hour, nocturia two to three times, and hesitancy and burning. The patient had been subjected to repeated gastrointestinal studies, stomach analysis, proctoscopic examinations, etc.

Physical examination was essentially negative except for tenderness over the left kidney. The urine was negative except for an occasional pus cell. Cystoscopy and pyelography revealed a large hydronephrosis of the left kidney with an obstruction at the ureteropelvic junction. Intravenous phthalein had an appearance time from the right kidney of 4 minutes and from the left kidney of 8 minutes; a fifteen-minute collection from the right kidney was 18 per cent; from the left kidney, 2 per cent. Blood urea was 39 mg. per cent. On June 14, 1932, the left kidney was exposed under spinal anesthesia. An obstruction was found at the ureteropelvic junction, and the posterior peritoneum and descending colon were intimately adherent to the anterior surface of the distended extrarenal pelvis. A plastic operation was performed, removing an elliptical piece of tissue from the anterior and posterior surfaces of the renal pelvis and the stricture at the ureteropelvic junction was corrected by a Heineke-Mikulicz repair. The patient made an uneventful recovery and was discharged from the hospital in two weeks.

Prior to operation, the patient's blood pressure varied between 200 and 210 systolic and 110 and 120 diastolic. Following operation, his blood pressure fell to 170/110 and remained at this level for three months. Three months following the operation, the patient developed a sudden sharp pain in the operative area following the lifting of a very heavy object. Two days later he presented a soft fluctuating mass in the upper end of the wound. Cystoscopic and pyelographic studies at this time revealed a rupture of the left kidney pelvis with an accompanying perinephritic abscess. A nephrectomy was done on Sept. 20, 1932. Almost the entire left adrenal gland was removed also. The patient made an uneventful recovery. Following this operation the patient returned for observation for a period of three years, during which time there was no recurrence of his gastrointestinal symptoms. The blood pressure prior to his second operation was 166/96 and following operation it declined to 154/90. Blood pressure determinations, which were made at the time of each office visit, showed slight fluctuation at or about the latter level. On May 20, 1935, his blood pressure was 152/108.

The pathologic specimen disclosed a small pin-point perforation at the site of previous plastic operation at the ureteropelvic junction. Immediately surrounding this area was a localized abscess in the peripelvic fat. On gross and microscopic examination the kidney showed the characteristic changes of acute and subacute

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Physical examination was essentially negative except for tenderness over the left kidney. The urine was negative except for an occasional pus cell. Cystoscopy and pyelography revealed a large hydronephrosis of the left kidney with an obstruction at the ureteropelvic junction. Intravenous phthalein had an appearance time from the right kidney of 4 minutes and from the left kidney of 8 minutes; a fifteen-minute collection from the right kidney was 18 per cent; from the left kidney, 2 per cent. Blood urea was 39 mg. per cent. On June 14, 1932, the left kidney was exposed under spinal anesthesia. An obstruction was found at the ureteropelvic junction, and the posterior peritoneum and descending colon were intimately adherent to the anterior surface of the distended extrarenal pelvis. A plastic operation was performed, removing an elliptical piece of tissue from the anterior and posterior surfaces of the renal pelvis and the stricture at the ureteropelvic junction was corrected by a Heineke-Mikulicz repair. The patient made an uneventful recovery and was discharged from the hospital in two weeks.

Prior to operation, the patient's blood pressure varied between 200 and 210 systolic and 110 and 120 diastolic. Following operation, his blood pressure fell to 170/110 and remained at this level for three months. Three months following the operation, the patient developed a sudden sharp pain in the operative area following the lifting of a very heavy object. Two days later he presented a soft fluctuating mass in the upper end of the wound. Cystoscopic and pyelographic studies at this time revealed a rupture of the left kidney pelvis with an accompanying perinephritic abscess. A nephrectomy was done on Sept. 20, 1932. Almost the entire left adrenal gland was removed also. The patient made an uneventful recovery. Following this operation the patient returned for observation for a period of three years, during which time there was no recurrence of his gastrointestinal symptoms. The blood pressure prior to his second operation was 166/96 and following operation it declined to 154/90. Blood pressure determinations, which were made at the time of each office visit, showed slight fluctuation at or about the latter level. On May 20, 1935, his blood pressure was 152/108.

The pathologic specimen disclosed a small pin-point perforation at the site of previous plastic operation at the ureteropelvic junction. Immediately surrounding this area was a localized abscess in the peripelvic fat. On gross and microscopic examination the kidney showed the characteristic changes of acute and subacute

and received treatment for tuberculous cystitis with methylene blue irrigations after the method of Brodney.

Prior to her operation, her blood pressure was 148/86. Upon discharge from the hospital on Dec. 8, 1936, her blood pressure was 120/80. Subsequent blood pressure determinations were made at regular intervals in the outpatient department and the blood pressure did not exceed 120/80. The last blood pressure reading was taken on Oct. 15, 1940.

The pathologist's report indicated an advanced case of renal tuberculosis with localized abscesses involving the upper major calyx and diffuse involvement of remaining kidney tissue. Moderate endarteritis of the blood vessels throughout the kidney was noted (grade 1+).

CASE 5.—(G. U., No. 91269.) D. P., 24 years of age, white, male, married, clerk, was admitted to the urologic ward of Sinai Hospital on May 4, 1937, complaining of pain in his right flank. The family history was negative for tuberculosis. Six years before, the patient had complained of pain in his right flank and cystoscopy and pyelography revealed a bilateral renal tuberculosis accompanied by tuberculosis of the prostate. Hospitalization was advised but was refused by the patient who remained in bed at home for five months with definite improvement. In January, 1936, he contracted a gonorrheal urethritis which responded promptly to treatment. In March, 1936, he developed a bilateral tuberculous epididymitis with an accompanying hydrocele on each side. He was treated by ultraviolet ray to scrotum and frequent tapping of the hydrocele, but two persistent fistulas developed on the left side of the scrotum. In October, 1936, a bilateral epididymectomy was performed. Following this operation the patient developed signs and symptoms of pulmonary tuberculosis (confirmed by x-ray) and was sent to a state sanatorium for tuberculosis in December, 1936, where he remained until one week before this admission to the hospital. During his stay in the sanatorium, sputum examinations were consistently negative and repeated x-ray of the chest showed a rapid improvement. In the last two months he had developed pain in his left hip and complained of persistent scrotal fistula. He had no urinary symptoms.

Examination disclosed tuberculous involvement of the prostate, both seminal vesicles, both vasa, and the left testicle. Two fistulas were present on the left side of the scrotum. There was no tenderness over either kidney. A chronic tuberculous osteomyelitis of the middle phalanx of the right third finger was present. Slight tenderness was present over the left buttock, but x-ray failed to show any bone involvement in this area. The lungs showed no signs of active tuberculosis on physical and x-ray examinations. The urine was negative except for 60 to 70 pus cells per high power field. Repeated examination of the urinary sediment by acid-fast staining failed to reveal any tubercle bacilli. The blood urea varied between 15 and 26 mg. per cent.

On May 5, 1937, intravenous urography revealed a normal kidney pelvis on the left side but definite signs of tuberculosis in the upper major calyces of the right kidney. Both ureters appeared normal. On May 14, 1937, cystoscopy and pyelography were performed and disclosed marked tuberculous changes involving the upper and middle major and minor calyces and the pelvis of the right kidney. Urine from the right kidney was negative for tubercle bacilli and on culture grew colon bacilli.

On May 21, 1937, a right nephrectomy was done under spinal anesthesia. Despite the fact that about 5 cm. of ureter was removed and no drains were employed at time of operation, the patient developed a postoperative fistula in the lumbar wound which persisted after discharge from the hospital on July 17, 1937.

losis occurred in 5 (13.5 per cent). The incidence of hypertension in cases with bilateral renal tuberculosis was not increased.

Crabtree and Chaset observed 1 case of tuberculous pyelonephritis with a preoperative hypertension of 154/105, and fourteen months following nephrectomy there was a reduction in blood pressure to 144/80.

CASE 3.—(Gyn., No. 4878.) A. B., 36 years of age, white, female, married, housewife, was admitted to the Sinai Hospital on Nov. 21, 1934, complaining of pain in the right upper quadrant and right lumbar region. The patient had been in good health until one year previously, when she developed pain in the right lumbar region and right upper quadrant radiating to the groin. The pain was unaccompanied by chills, fever, nausea, or vomiting. She also complained of diurnal frequency and nocturia. Hematuria was also present two months before for the first and only time. In the past year the patient had received cystoscopic treatments from another doctor with slight improvement.

Blood urea was 26.36 mg. per cent. Urine showed many pus cells. Combined intravenous phthalein yielded 60 per cent for the first hour and 15 per cent for the second hour. Cystoscopy and pyelography revealed a nonfunctioning pyonephrotic kidney on the right side. Cultural and staining studies failed to reveal tubercle bacilli in the urine. On Dec. 7, 1934, a right nephrectomy was done under ether anesthesia. The patient made an uneventful recovery and was discharged from the hospital on Dec. 24, 1934.

Blood pressures were taken daily prior to the operation and revealed a systolic pressure to fluctuate between 160 and 168 and the diastolic, between 90 and 100. Following operation the blood pressure gradually fell to 140/90 and remained at this level for the next two years, while she was under the observation of her family physician.

Pathologic diagnosis was (1) tuberculous pyonephrosis and (2) chronic recurrent pyelonephritis. Characteristic tubercles and abscesses were found as well as extensive degenerative and atrophic changes in the glomeruli, tubules, and interstitial tissue. The sclerotic changes in the walls of the smaller renal vessels were moderately advanced and were classified as 2+.

CASE 4.—(Gyn., No. 5651.) D. L., 21 years of age, white, female, married, housewife, was admitted to the Sinai Hospital on Oct. 14, 1936, complaining of frequency of urination. Her family history was negative. The patient had enjoyed good health until 1935, when symptoms of tuberculosis developed and she was sent to a sanatorium, where she spent six months and was discharged as an arrested case. For the past eight months the patient has complained of dull pain in the right lumbar region with diurnal frequency, burning and smarting on urination. In the past two months she has had an increase in symptoms, accompanied by pyuria and hematuria.

Examination revealed signs of a healed tuberculosis in both apices and tenderness over the right kidney. Urine showed 1+ albumin and many pus cells with clumps. Urinary sediment was stained for tubercle bacilli, but none were found. Blood urea was 31.06 mg. per cent. Cystoscopy and pyelography revealed numerous areas of hemorrhagic infiltration throughout the right half of the bladder. The right ureteral orifice had a typical "golf hole" appearance. Pyelography showed tuberculous ulceration of the upper major calyx of the right kidney. The left kidney appeared normal.

On Nov. 13, 1936, a right nephrectomy was done under ether anesthesia. The postoperative course was uneventful, and the wound healed per priam. Following her discharge from the hospital, the patient returned to the outpatient department

and received treatment for tuberculous cystitis with methylene blue irrigations after the method of Brodney.

Prior to her operation, her blood pressure was 148/86. Upon discharge from the hospital on Dec. 5, 1936, her blood pressure was 120/80. Subsequent blood pressure determinations were made at regular intervals in the outpatient department and the blood pressure did not exceed 120/80. The last blood pressure reading was taken on Oct. 15, 1940.

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localized to a particular portion of the kidney with a minimum degree of renal damage.

4. A reluctance on the part of most physicians to report unusual case reports.

In their series of 56 cases of hypertension associated with renal diseases, Schroeder and Steele found 8 cases of renal calculi accompanied by hypertension and obtained a previous history of renal calculus or colic in 4 other patients. Maher and Wosika encountered 18 cases of renal calculi in their series of 101 cases of primary urinary tract pathology associated with hypertension. Longcope described a case of hypertension in an individual in whom a chronic renal infection accompanied a calculus imbedded in a calyx. Walters and Barker, Mulholland, and Nesbit and Ratliff reported cases of hypertension due to unilateral pyelonephritis secondary to renal calculi successfully treated by nephrectomy. Bothe reported a case of calculous pyonephrosis with hypertension which showed a slight improvement following nephrectomy.

It is also well to bear in mind that pathologic changes in or about the kidney other than pyelonephritis may develop and produce severe damage to the kidney parenchyma or to the vascular supply. A severe infection associated with a calculus in the kidney or ureter may cause extensive inflammatory or fibrotic changes in and about the kidney, pelvis, and ureter which may seriously interfere with the blood supply to these structures or act as an obstruction to outflow of urine. Such changes, which are prone to occur following the operative removal of stones from these structures as a natural sequela or as the result of faulty drainage, may lead to renal ischemia and subsequently influence the development of hypertension.

An example of the serious damage which may result from a ureteral calculus is demonstrated by the case reported by Hyman, and subsequently referred to by Oppenheimer, Klemperer, and Moschkowitz. A ureterolithotomy was performed in a male 30 years of age, which was followed two years later by pyelonephritis, hypertension, headaches, and retinal changes. Nephrectomy resulted in a cure. The striking pathologic finding was a marked sclerosis of the renal artery whose lumen was almost three-fourths occluded. Von Monakow also reported a case of ureteral calculus accompanied by an elevation in blood pressure to 170 mm. Hg which fell to 112 mm. after removal of the stone. Schroeder and Fish described a case of arterial hypertension which ran a malignant course and was associated with bilateral organic renal disease. The left kidney which was removed contained a calculus, chronic pyelonephritis and a hydronephrosis due to an aberrant vessel constricting the ureteropelvic junction. A slight hydronephrosis was present on the right. Nephrectomy did not influence the rapid downhill course. Marked arteriolar changes were present in the left kidney with slight

Prior to operation his blood pressure varied between 144 and 150 systolic and 92 to 96 diastolic. Following operation the blood pressure fell to 130/90 at time of discharge. On June 6, 1937, the consulting ophthalmologist reported marked congestion and tortuosity of the retinal veins, which were considered early hypertensive changes.

Following discharge from the hospital the patient returned to the sanatorium. The right lumbar persisted and drained a very slight amount of seropurulent material. Three serotal sinuses were present and appeared to lead to the left testicle which was nodular. He was readmitted to the hospital on May 9, 1938. A left orchidectomy and excision of the fistulous tract was performed and primary wound healing obtained prior to his discharge on May 21, 1938. During this stay in the hospital his blood pressure never exceeded 122/78. Subsequent blood pressure determinations, taken by his family physician in the last two years, disclosed no elevation above 120/78.

Pathologic examination of the right kidney revealed a fairly well advanced tuberculous pyonephrosis. Caseating abscesses were found throughout the entire kidney but were more pronounced in the upper pole. Sclerotic changes (grade 2+) were found in the walls of some of the smaller blood vessels in the parenchyma.

*C. Chronic Infections of Kidney Complicating Other Lesions of Kidney.*—Hypertension has been described in individuals suffering from a variety of noninfectious diseases of the kidney; viz., renal calculi, obstructive uropathies, congenital anomalies of the kidney, etc. If a careful study of such cases were made, undoubtedly one would find in the majority of instances either a concomitant chronic infection or a history of an antecedent, intermittent, or recurrent infection whose occurrence has been forgotten by the patient and overlooked by the physician. Ample clinical evidence in support of this contention is found in the high incidence of chronic infection (pyelonephritis) in cases of renal calculi and obstructive uropathies, and in either case the end picture may be a contracted and scarred kidney of chronic pyelonephritis or a pyonephrotic kidney of varying size.

In view of the close relation between chronic pyelonephritis and calculi, one would expect to find reports of more cases of renal calculi accompanied by hypertension. The paucity of such reports may be due to any of the following reasons:

1. In the case of renal calculus, pain is an early but prominent feature of the disease which demands relief before infection or sufficient renal damage is permitted to occur and initiate those pathologic changes conducive to hypertension.

2. In chronic cases the presence of a calculus and infection is entirely overlooked or disregarded as the clinician's attention is focused on the hypertension. On the other hand, the urologist may overlook or fail to recognize the presence of hypertension, as his efforts are directed toward removal of the stone, eradication of the infection, or alleviation of the pain.

3. In some cases the location of the calculus or the character of the infection associated with the calculus may produce pathologic changes

localized to a particular portion of the kidney with a minimum degree of renal damage.

4. A reluctance on the part of most physicians to report unusual case reports.

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but similar changes in the right kidney. Everett reported a case of ureteral calculus accompanied by a pyelonephritic contracted kidney of long standing in which a reduction of hypertension followed nephrectomy.

Bothe noted a slight reduction in blood pressure following the removal of a calculous pyonephrotic kidney associated with an angulation of the upper ureter due to a fibrous band in a female, aged 53 years, who had had high blood pressure for years and suffered a paralytic stroke five months prior to operation. Her preoperative blood pressure ranged between 174 and 202 mm. systolic and 104 and 148 mm. diastolic, but following operation her general condition improved considerably and her blood pressure fell to 140/80 one week after discharge from the hospital.

Brausch, Walters, and Hammer observed hypertension in 161 cases (20.3 per cent) of 793 patients operated upon for stone; i.e., hydro-nephrosis with stone, stone with renal infection, stone without renal infection. They emphasized the important role of secondary infection in the production of hypertension in these cases which is substantiated by the fact that hypertension was present in 22.5 per cent of cases with infection as compared to 5.7 per cent without infection. They maintained that the deciding factor was not the degree of infection but the presence of vascular sclerosis and parenchymal atrophy. The incidence of hypertension in bilateral nephrolithiasis was no greater than in unilateral nephrolithiasis. It was interesting to note that in 8 (20 per cent) of 20 cases of atrophic pyelonephritis with hypertension, nephrolithiasis antedated the other conditions.

The postoperative course of the blood pressure was studied in 189 cases of which 111 had preoperative hypertension and 78 had a normal preoperative blood pressure. In the group of 111 cases with preoperative hypertension, the blood pressure returned to normal after operation in 25 cases, returned to normal for six months to two years but subsequently became elevated in 10 cases, and was uninfluenced in 76 cases. In the group of 78 cases with normal blood pressure before operation, hypertension developed following a conservative operation in 10 cases, several of whom required secondary nephrectomy before the blood pressure returned to normal.

CASE 6.—(Gyn., No. 1714.) S. D., 48 years of age, female, white, married, housewife, was referred to me for urologic study on April 10, 1939. The family history was unimportant. She had enjoyed good health until thirteen years previously, when she developed a right renal colic which recurred at intervals of from one to three months until November, 1938, when a urologic study was done elsewhere and a diagnosis of *right renal calculus* was made. The calculus was removed by operation. In January, 1939, the patient developed signs and symptoms of acute infection of the right kidney and bladder which had persisted to date despite treatment with various drugs; i.e., mandelic acid, pyridium, sulfanilamide, etc. In the last month she had severe pain localized to the right kidney area accompanied by chills, fever, nausea, vomiting, urinary frequency, burning, pyuria, etc. The

patient also complained of frequent headaches and dizzy spells in the three or four months before admission. She stated that she had been treated for "high blood pressure" the past three years.

Examination disclosed tenderness over the right kidney with a positive right ureteral point. Blood pressure varied between 188/100 and 210/110. Cystoscopy and pyelography were performed. A differential phthalein revealed appearance time from the right kidney to be 4 minutes as compared to three minutes from the left. Fifteen-minute collections from kidney showed the right kidney to be 8 per cent and the left kidney, 20 per cent. A diagnosis of staghorn calculus of the right kidney with chronic recurrent pyelonephritis (*Bacillus coli*) was made. There was an abnormal angulation at the right ureteropelvic junction which probably developed after previous operation and was responsible for the recurrent stone formation and the persistence of the renal infection.

On Apr. 25, 1939, a right nephrectomy was done. The patient made an uneventful recovery and was discharged from the hospital on May 20, 1939. During the last week of her hospital stay the blood pressure varied between 124 and 138 systolic and 60 to 70 diastolic. On Feb. 21, 1940 (ten months after operation), the blood pressure was 152/86, and on May 29, 1940 (thirteen months after operation), 158/92.

The pathologic diagnosis was (1) chronic pyelonephritis, (2) renal calculus, and (3) kidney infarcts. A marked thickening of the walls of the smaller blood vessels was noted with occasional obliteration of some arterioles. The changes were graded 2+.

CASE 7.—(G. U., No. 1681.) J. C., 49 years of age, male, white, married, salesman, was admitted to the Sinai Hospital on Apr. 23, 1935, complaining of pain in his left kidney region and hematuria of two weeks' duration. On April 1, 1932, he had had a left nephrolithotomy for renal calculi. Following this operation, he was asymptomatic until 2 weeks before this admission.

Physical examination disclosed chronic bronchitis and bronchiectasis in addition to tenderness over the left kidney. His blood pressure on admission was 168/88, and prior to operation varied between 166 and 174 systolic and 84 and 92 diastolic. The urine revealed 50 pus cells, occasional red blood cell per high-power field, and colon bacilli. The blood urea nitrogen was 15.12 mg. per cent and combined phthalein excretion was 50 per cent for the first hour and 10 per cent for the second hour. Ophthalmoscopic examination was not done. Cystoscopy and pyelography revealed a nonfunctioning left kidney containing a large staghorn calculus. Phthalein excretion from the right kidney was 30 per cent in fifteen minutes but none from the left kidney in same time interval.

On Apr. 26, 1935, a transperitoneal left nephrectomy was done; the patient made an uneventful recovery, except for hiccoughing which was successfully combated and for a disruption of the wound requiring secondary closure. He was discharged on June 11, 1935 (forty-seventh postoperative day). Prior to discharge the blood pressure was 140/80. The patient returned for periodic examination to his family physician, who reported that his blood pressure taken on July 15, 1935, was 132/80 and had remained at about the same level during the next three years that he was under observation.

The pathologic diagnosis was (1) chronic pyelonephritis and (2) nephrolithiasis. In addition to the characteristic lesions of chronic pyelonephritis, slight endarteritic changes were noted in the walls of the smaller blood vessels which were graded 1+.

CASE 8.—(G. U., No. 1668.) J. R., 52 years of age, white male, married, bartender, was first seen in my office on Feb. 5, 1939, complaining of pain in his right

lumbar region for the previous ten days. Family history was negative. He had enjoyed good health until 1930, when he had a stone removed from his right kidney. For the previous three years he had been receiving treatments for a chronic prostatitis. The patient stated that he had been treated for the usual symptoms of "high blood pressure" for the past two years. At present he complained of dull intermittent pain in the right kidney region, urgency, frequency, nocturia. There was no hematuria or colic.

Examination disclosed tenderness over the right kidney, anteriorly and posteriorly, and a mild degree of chronic prostatitis. Ophthalmoscopic examination revealed moderately advanced changes in retinal vessels indicative of hypertensive disease. Blood pressure was 192/110. Voided specimen of urine showed a trace of albumin and microscopically 8 to 10 pus cells per high-power field. Cystoscopy and pyelography revealed a group of three small stones in the lower major calyx of the right kidney which showed the typical pyelographic changes characteristic of chronic atrophic pyelonephritis. The right ureter appeared to angulate at the ureteropelvic junction. Fractional differential phthalein test revealed the appearance time from the right kidney to be 18 minutes and from the left kidney to be 3 minutes; a fifteen-minute collection from the right kidney was 0 and from the left kidney was 18 per cent. A diagnosis of right chronic atrophic pyelonephritis with nephrolithiasis and hypertension (Goldblatt type) was made.

The patient was admitted to the Sinai Hospital on March 13, 1939. Blood pressure determinations were done daily and ranged between 192 and 196 systolic and 110 to 114 diastolic. Two electrocardiographic examinations were made and were reported negative. On March 13, 1939, right nephrectomy was performed. His blood pressure fell to 162/100 on March 22, 1939, and to 158/100 on March 27, 1939, when he was discharged from the hospital.

The wound continued to drain a slight amount of seropurulent material, and the patient was readmitted to the hospital. The source of the persistent infection in the wound was found to be in the right ureter and on June 9, 1939, a right ureterectomy was performed and the wound healed per primam. He was discharged from the hospital on June 23, 1939, at which time his blood pressure had fallen to 134/80. The patient subsequently reported to the outpatient clinic at regular intervals, and blood pressure determinations were made which varied from 134 to 140 systolic and 80 to 110 diastolic. The last recording was 140/108 on April 13, 1940 (thirteen months after nephrectomy).

The pathologic diagnosis was (1) chronic pyelonephritis (2) renal calculi, and (3) renal infarcts. Typical changes of chronic pyelonephritis were present throughout the kidney. Hyalinization of the glomeruli was especially marked. Sclerotic changes in the walls of the cortical vessels were rather striking for many vessels showed complete obliteration and fibrotic replacement. The vascular changes were graded 2+.

CASE 9.—(Gyn. No., 99629.) R. C., 38 years of age, female, white, married, housewife, was admitted to the Sinai Hospital on Dec. 3, 1938, with a complaint of pain in her right lumbar region of two months' duration. Family and past histories were negative, except that the patient had been treated in the psychiatric and endocrinological outpatient departments in the previous five years for various physical and mental maladjustments. Five days before admission she had had an attack of right renal colic with hematuria which persisted until admission to the hospital.

Examination revealed an obese female of low mentality with marked spasticity, rigidity, and tenderness over the right kidney. A medical consultation was obtained, and the following diagnosis was made: (a) hypertensive cardiovascular disease, (b) renal calculus with polyglandular dyscrasia (moron), and (c) moron.

The eye grounds were reported negative. Her blood pressure was taken daily for the first week and varied between 160 and 164 systolic and 100 and 104 diastolic. The urine was negative except for many pus cells and red blood cells. Blood urea was 21.57 mg. per cent. Basal metabolism was 9. Cystoscopy and pyelography disclosed a large calculous pyonephrotic right kidney. Fractional differential phthalein showed a normal appearance time from each kidney, but the 15-minute excretion from the right kidney was 3 per cent against 15 per cent from the left kidney.

On Dec. 15, 1938, a right nephrectomy was done. The patient had an uneventful recovery and was discharged on Jan. 8, 1939. Following operation the blood pressure fell to 120/64 and prior to discharge from the hospital was 120/80. The patient returned to the outpatient clinic for observation where the following blood pressure determinations were made: May 2, 1939 (four and one-half months postoperatively), 170/120; May 16, 1939 (five months postoperatively), 180/110; Aug. 2, 1939 (eight months postoperatively), 150/98; Oct. 10, 1940 (twenty-two months postoperatively), 146/100. On May 8, 1939, ophthalmoscopic examination revealed no signs of nephritis or hypertension.

The pathologic diagnosis was (1) pyonephrosis and (2) multiple renal calculi. Histologic studies revealed changes characteristic of a well-advanced pyonephrosis; viz., abscess formation, fibrosis, granulation tissue, round-cell infiltration, degenerative and atrophic changes in the glomeruli and tubules, and hemorrhagic infiltrations. Sclerotic changes in the walls of the smaller renal vessels were readily discernible and graded 1+.

CASE 10.—(Gyn., No. 8076.) R. G., 51 years of age, white female, married, housewife, was admitted to the Sinai Hospital on Nov. 9, 1938, complaining of pain in the left kidney region. The family history was unimportant. She had had an appendectomy and suspension of the uterus in 1923. In May, 1928, she was admitted to the hospital and treated for hypertension and migraine, during which time the blood pressure varied from 218/130 to 162/102. In February, 1934, the patient had a right pyelolithotomy performed.

For the past two years the patient had complained of dizziness, headaches, nausea, vomiting, paroxysmal nocturnal dyspnea, loss of weight, oliguria, nocturia, and frequency. Physical examination revealed hypertensive cardiovascular disease, cardiac hypertrophy, and a hernia of the right kidney incision. Ophthalmoscopic examination revealed moderately advanced hypertensive changes of the retinal arteries.

Cystoscopy and pyelography revealed a calculous pyonephrosis on the right. The fractional phthalein showed 2 per cent excretion from the right kidney and 18 per cent from the left kidney in fifteen minutes. Urine showed a faint trace of albumin and microscopically a few pus and red blood cells and rare cast, and many colon bacilli. The blood urea was 45.53 mg. per cent. Combined phthalein test showed 20 per cent excretion for the first hour and 10 per cent for the second hour.

On Nov. 12, 1938, the right kidney was removed. During the convalescence, the blood pressure fell from the preoperative level of 220/120 to 140/90. The patient was discharged on Dec. 4, 1938.

Following discharge from the hospital, the patient was observed in the outpatient department. Her blood pressure gradually increased above the preoperative level, and on March 12, 1939, the reading was 220/124. She was readmitted to the Sinai Hospital on Dec. 20, 1939, with typical signs and symptoms of an advanced hypertensive cardiovascular disease with marked impairment of renal function. All of the clinical symptoms noted above were increased in severity. Her blood pressure on admission and for several days thereafter varied between 230 and 245 systolic and 126 to 135 diastolic. Ophthalmoscopic examination showed

a marked increase in the extent and severity of the hypertensive changes in the retinal arteries. Plain plate of the genitourinary tract showed no radiable shadows, but there was a decided decrease in the size of the left kidney. The blood chemistry at this time showed serum protein, 6.33 mg. per cent; albumin, 3.94 mg. per cent; globulin, 2.41 mg. per cent; blood chlorides, 536 mg. per cent; urea, 218.19 mg. per cent; creatinine, 3.99 mg. per cent; calcium, 11 mg. per cent; and  $PO_4$ , 3.6 mg. per cent. She had a marked anemia with hypochromia with a hemoglobin of 10 Gm. (58 mg. per cent); white blood count was 7,800; combined phthalein showed total excretion of 5 per cent for the first hour and 0 per cent for the second hour. With rest in bed and other supportive measures, including frequent intravenous injections of glucose, there was a slight reduction in blood pressure to 210/120. However, in view of extensive hypertensive cardiovascular damage and seriously impaired renal function, the prognosis was poor.

II. OBSTRUCTIVE LESIONS OF THE UPPER URINARY TRACT.—In the latter half of the nineteenth century, a period in which accurate blood pressure determinations were not available, one finds an occasional reference to the occurrence of cardiac hypertrophy (i.e., hypertension) in cases of obstructive lesions of the genitourinary tract. This pathologic complication was first pointed out by Friedreichs in 1853 in a case of hydronephrosis and was subsequently observed by Potain in 1875 in prostatic enlargement, by Cohnheim in 1877 in bilateral ureteral obstruction due to a huge vesical calculus, by Strauss in 1882 in ureteral obstruction resulting from a carcinoma of the uterus, and by Weill in chronic cystitis with ascending infection of both kidneys.

In the past twenty years urologists have recognized the frequent occurrence of hypertension in various obstructive lesions of the urinary tract. In 1906, Passler reported a case of anuria of twelve days' duration, resulting from partial occlusion of both ureters by infiltrations from a carcinoma of the cervix. In 1911, Braasch described three cases of carcinoma of the uterus with infiltration of the broad ligaments and compression of both ureters. During the periods of anuria, the blood pressure rose sharply but fell to normal when the urinary obstruction was relieved by ureteral catheterization. The beneficial effects of preliminary bladder drainage in cases of hydronephrosis with hypertension due to prostatic hypertrophy was first pointed out by von Monakow and Mayer in 1918, and subsequently in 1920 and 1923 by O'Connor, and in 1936 by Ritch. In 1933, Abeshouse pointed out that in patients with acute retention of urine, the blood pressure, especially the systolic, is frequently elevated and gradually recedes with the institution of decompression and drainage. Abeshouse also stressed the fact that not all hypertensive patients had a lowering of the blood pressure upon relieving the obstruction, but the number of patients so developing a lowering of blood pressure suggested prostatic obstruction as one of the causes of hypertension.

The occurrence of hypertension in obstructive lesions of the upper urinary tract was investigated in 1917 by Lohlein, who described 2

cases of hydronephrosis accompanied by elevations in the blood pressure as high as 210/140, and in 1936 by Ritch, who described the beneficial effects of conservative urologic treatment in 5 cases of hydronephrosis due to various causes; i.e., ureteral strictures, ureteral kinks, ptosis, etc. Fishberg noted a marked reduction in hypertension following the use of an indwelling catheter in a case of tabetic paralysis of the bladder.

The significance of hydronephrosis as an etiologic factor in the production of hypertension is forcibly brought out by the recent statistical studies on the incidence of the various genitourinary lesions in cases of essential hypertension. In the 101 cases reviewed by Maher and Wosika, the frequency of primary obstructive lesions was as follows: prostatic obstruction, 31 cases; prolapse of uterus with hydronephrosis, 7 cases; diverticula of bladder, 5 cases; urethral stricture (male), 4 cases; carcinoma of bladder with ureteral obstruction, 2 cases; bladder stone, 1 case; and vesicovaginal fistula, 1 case. Schroeder and Steele demonstrated the presence of some primary abnormality in the urinary tract by intravenous urography in 50 of 71 cases of essential hypertension. In 36 cases the lesion was either a unilateral or bilateral hydronephrosis due to various types of obstruction. Oppenheimer, Klemperer, and Mosechkowitz noted the occurrence of hypertension in 21 (32 per cent) of 66 cases of unilateral hydronephrosis or chronic pyelonephritis; the latter grouping was made because of the frequent association of the two lesions.

*A. Hydronephrosis.*—In a discussion of the pathogenesis of hypertension in obstructive lesions of the urinary tracts, we are not particularly concerned with the site or cause of the obstruction, for the effect on the upper urinary tract is practically the same in all instances. Urologists are familiar with the clinical and pathologic changes produced by simultaneous complete or partial obstruction of one or both ureters. However, the clinician, in the absence of roentgenologic and urologic investigation, may easily confuse the picture with chronic nephritis. The clinical diagnosis may be further complicated by presence of infection which may overshadow the effects of obstruction. This is particularly true in the case of chronic bilateral ureteral obstruction of moderate degree as pointed out by Scholl. He has also emphasized the fact that extensive destruction of the renal parenchyma is rarely caused by infection but is usually accompanied by some degree of obstruction in the urinary tract.

We are greatly indebted to Hinman for his comprehensive studies on the pathogenesis of hydronephrosis. He has employed the term hydro-nephrotic atrophy to denote the usual changes of pelvic dilatation and parenchymal atrophy following any type of urinary obstruction and considered it to be essentially a pressure and anemic atrophy. He differentiated this type from (a) primary atrophy in which the atrophy occasionally develops following a complete obstruction without dilatation

of the pelvis and tubules of the kidney; and (b) secondary atrophy in which changes due to infection or disuse are superimposed upon the above two types. In the development of hydronephrotic atrophy, four factors are involved; viz., pressure, anemia, degeneration, and disuse. Pressure is undoubtedly the primary factor, but anemia or ischemia plays the most important role once the process is initiated.

By studying the injected arterial tree, Hinman demonstrated that in hydronephrosis the circulatory changes are produced by mechanical displacement acting by compression or stretching according to the course of the vessels in relation to the direction of the pressure. As the pressure from the distending pelvis is transmitted to the parenchyma, the larger vessels become attenuated by stretching and a diminution of the flow of blood to and from the cortex ensues with a resulting partial anemia of the cortical parenchyma. The latter changes tend to lessen the normal tissue tone and favor a relaxation which is conducive to further changes by the process of distention.

The effect of this partial ischemia upon the development of hypertension is not known, but judging from the absence of hypertension in the vast number of cases of uncomplicated hydronephrosis, one may infer that there is little clinical evidence of such a relation. However, when the pathologic process of pressure and atrophy advance to the stage of renal insufficiency or when infection is superimposed, the likelihood of hypertension's developing becomes greater. Many of the obstructive uropathies, irrespective of the site or degree of the primary obstruction, are accompanied by pyelonephritis and calculi which have been shown to have a close etiologic relation to hypertension.

**B. Pyonephrosis.**—Some degree of infection usually occurs in practically every case of advanced hydronephrosis. The symptoms resulting from such an infection may be so severe or annoying that urologic investigation is instituted and a hitherto unsuspected and infected hydronephrosis revealed. Infection is particularly prone to occur in cases of hydronephrosis caused by calculi in the renal pelvis. The pathology of an infected hydronephrosis is essentially a pyelonephritis involving the pelvic mucosa as well as the parenchyma. The infectious process may spread and cause extensive suppurative changes in the parenchyma, producing a pyonephrosis.

Quinby reported a case of severe hypertension (systolic pressure of 250 mm. Hg) in a boy 14 years of age, caused by bilateral hydronephrosis and chronic pyelonephritis. Following the removal of a severely damaged kidney, the patient remained free from hypertension for ten years, but the following year the hypertension recurred. Hinman observed a similar case in a boy of 18 years of age, who had a systolic pressure of 218 mm. and died of uremia without any operation. Fishberg described a case of congenital bilateral hydroureter and hydro-nephrosis caused by a congenital valvular obstruction in the urethra and

accompanied by hypertension. I have encountered a similar case in a 19-month-old boy, whose blood pressure before cystoscopic excision of the valves and left nephrectomy was 128/85 and during the period of postoperative convalescence fell to 108/65. Unfortunately a follow-up study of the blood pressure could not be obtained as the boy's parents moved to a distant city and could not be contacted. Relatives informed me that the boy has shown a remarkable improvement two years later. This case is not included in Table III.

Morton observed a marked fall in blood pressure following the removal of a hydronephrotic kidney caused by an anomalous blood vessel. Similar results have been obtained by Ritch, Nesbit and Ratliff, and Bartels and Leadbetter. Everett reported three interesting cases of hydronephrosis in whom a reduction in hypertension followed operation: (1) a colored female, aged 26 years, who had a large fibroma enucleated from the left iliac fossa, and ligation of the left ureter performed one year prior to the left nephrectomy for hydronephrosis complicated by chronic pyelonephritis; (2) a female, aged 37 years, who had a left nephrectomy for hydronephrosis with an old pyelonephritis and extensive atrophy of the left kidney and marked vascular sclerosis; and (3) a female, aged 36 years, who was subjected to a ligation of an aberrant vessel and resection of a large extrarenal pelvis in a case of a large hydronephrosis produced by obstruction of the ureteropelvic portion of the ureter by the aberrant vessels.

Bothe reported a case of hypertension (174/120) in a 3-year-old boy associated with bilateral hydronephrosis (more marked on the left) and complete stenosis of the left ureteral orifice. Following a suprapubic operation in which the left ureteral orifice was incised and the lower ureter freed, the blood pressure was greatly reduced (114/54).

Braasch, Walters, and Hammer observed a low incidence of preoperative hypertension; viz., 51 cases (13.7 per cent) in a series of 372 cases of hydronephrosis without stone. Hypertension occurred in only 7.7 per cent of patients under 50 years of age as compared with 38.9 per cent of patients over 50 years. The size of the hydronephrotic sac and the degree of pyelectasis did not appear to be factors in the production of hypertension. They believed that the deciding factors were the resulting sclerotic and atrophic changes in the renal parenchyma. They studied the postoperative course of the blood pressure of 73 patients operated upon for hydronephrosis without stone. In this group 29 had hypertension preoperatively, and following operation, the blood pressure returned to normal in 10 cases (34.4 per cent) and remained so for from one to five years. Eight of these patients had a nephrectomy and two, a conservative operation. The hypertension persisted in 16 of the 29 cases treated by nephrectomy. In 42 cases the blood pressure was normal before and after operation, and in 2 other cases the blood pressure was normal before operation, but following operation hypertension developed. The preoperative hypertension, which

was present in 4 cases of bilateral hydronephrosis, was not affected by surgical drainage. However, hypertension developed in 2 cases of bilateral hydronephrosis in which one kidney was suddenly occluded, and following renal drainage, the blood pressure returned to normal in one case.

CASE 11.—(G. U., No. 1383.5.) J. B., white, male, 8½ years of age, was admitted to the surgical pediatric ward of the Sinai Hospital on May 3, 1933, complaining of pain in the right half of the abdomen of fourteen hours' duration. His family and past histories were essentially negative. About five days prior to admission to the hospital, the patient had a sore throat which cleared up with usual family remedies. On the morning of admission, the patient complained of dull pain in the right half of his abdomen, accompanied by nausea but no vomiting. His mother gave the patient a dose of epsom salts and later applied an ice bag to the right abdomen. Since pain persisted the mother brought the child to the hospital. She stated that two years before the patient had had a similar episode of pain in his right abdomen which persisted for one week and subsided with ice bags.

Examination disclosed a moderately distended abdomen with marked tenderness over the entire right upper and lower quadrants with a round tender mass about 10 cm. in diameter in the right upper quadrant. Leucocyte count was 8,000 with 76 per cent polymorphonuclear cells. The urine was negative except for an occasional pus cell. After much deliberation and consultation between the surgical and pediatric consultants, a tentative diagnosis of intussusception producing an incomplete intestinal obstruction was made in full cognizance that the laboratory findings did not support or confirm such a diagnosis. Exploratory laparotomy was performed, no intraperitoneal pathology was found, and a normal appendix was removed. The right kidney fossa was found to be occupied by a soft, fluctuant, cystic mass about 12 cm. in diameter, which was considered to be a multilocular pyonephrotic kidney.

On May 16, 1933, the patient was transferred to the urologic service. Cystoscopy and pyelography revealed a nonfunctioning multilocular pyonephrotic kidney on the right. The blood urea varied between 32.36 and 39.55 mg. per cent. A combined phthalein test showed 50 per cent excretion in the first hour and 25 per cent in the second hour. On June 16, 1933, a right nephrectomy was done. The operative specimen showed a large multilocular pyonephrotic kidney with a dense stricture of the ureter about 1 cm. below the ureteropelvic junction. The patient made an uneventful recovery. He was discharged from the hospital on June 28, 1933.

During his stay in the hospital a daily blood pressure record was kept. Prior to nephrectomy the blood pressure varied from 140/84 to 160/100. Following nephrectomy the blood pressure fell to 135/80. He was followed in the outpatient clinic for several years. The blood pressure gradually diminished to 120/80. The last blood pressure was recorded on Oct. 17, 1940, as 120/82.

The pathologic diagnosis was (1) multilocular hydronephrosis and (2) chronic pyelonephritis. Numerous areas of diffuse and focal leucocytic infiltrations were found scattered throughout the kidney parenchyma in addition to atrophic and degenerative changes in the tubules and glomeruli. The vascular changes were of a relatively mild degree (grade 1+).

CASE 12.—(G. U. No. 1945.) G. J., 56 years of age, white, married, male, iron and steel worker, was admitted to the Sinai Hospital on June 30, 1936, for pain in his left kidney region and hematuria. His family and past histories were unimportant. He had had left renal colic four weeks previously and had noticed blood in his urine on several occasions thereafter.

Physical examination was essentially negative except for tenderness in the left kidney region, cardiac hypertrophy, and hypertension (180/120). Unfortunately an ophthalmoscopic examination was not done. Urine examination disclosed 2+ albumin with 8 to 10 pus cells and 10 to 15 red blood cells per high-power field. Blood urea nitrogen was 24.64 mg. per cent. Cystoscopy, pyelography, and a differential phthalein test were performed and a diagnosis of nonfunctioning left pyonephrosis was made. On July 1, 1936, a left nephrectomy was done and the patient made an uneventful recovery, being discharged from the hospital on the twelfth postoperative day, when the blood pressure was 140/90.

The patient was under observation for the next ten months. The red and white blood cells disappeared from the urine, likewise the albumin. His blood pressure varied between 140 and 144 systolic and 90 and 92 diastolic. The patient was lost sight of until Oct. 13, 1940, when he reappeared for examination. The blood pressure was 170/110. The urine gave a positive test for albumin and on microscopic examination showed no red blood cells or pus cells but an occasional hyaline cast. Ophthalmoscopic examination revealed dilation and tortuosity of the retinal vessels. The patient stated that in the past six months he had been troubled with headaches, weakness, dizzy spells, and dyspnea.

The pathologic diagnosis was (1) pyonephrosis and (2) chronic pyelonephritis. Characteristic degenerative changes, such as fibrosis, necrosis, abscess formation, hyalinization, acute and chronic inflammatory infiltrations, etc., were found throughout the kidney. The large renal vessels at the hilum were thickened and the smaller vessels throughout the kidney parenchyma showed chronic degenerative changes in their walls varying from slight fibrosis to complete obliteration (grade 3+).

CASE 13.—(G. U., No. 1175.5.) M. K., 51 years of age, white, male, married, tailor, was admitted to the urologic ward of the Sinai Hospital on Feb. 9, 1932. In November, 1931, he had developed signs and symptoms of a stone in his right kidney, and a right nephrolithotomy was performed. The patient made an uneventful recovery except for a small fistula, which was present at the time of this admission to the hospital. He also complained of urgency, frequency, and burning. He had gained 20 pounds in weight. The patient was also treated for diabetes.

Physical examination was essentially negative except for tenderness over the right upper quadrant and right lumbar region. A small fistula was present in the upper end of the lumbar incision. Combined intravenous phthalein yielded 45 per cent for the first hour and 10 per cent for the second hour. Urine showed a trace of albumin and 1+ sugar and an occasional pus cell. Blood urea was 35.95 mg. per cent, and his blood sugar was 121 mg. per cent. Cystoscopy and pyelography revealed a nonfunctioning pyonephrotic kidney on the right side. On Feb. 16, 1932, a right nephrectomy was done under spinal anesthesia. The patient made an uneventful recovery and was discharged from the hospital on Mar. 8, 1932.

Prior to operation his blood pressure varied between 184 and 188 systolic and 110 and 114 diastolic. Following operation the blood pressure gradually fell to 152/92 prior to discharge from the hospital. For the next two years he returned to the outpatient department for observation and his blood pressure declined to 142/90 and remained at that level.

The pathologic diagnosis was pyonephrosis. Numerous recent and old abscesses were scattered throughout the scarred kidney. Several infarcts of varying size were present. Sclerotic changes in the walls of the smaller renal vessels were quite marked (grade 2-).

C. *Nephroptosis*.—It is highly probable that in cases of hydronephrosis associated with acquired nephroptosis, the development of partial

renal ischemia may be considerably influenced by other vascular changes incidental to the nephroptosis. These vascular changes include (a) elongation, narrowing, or compression of renal vascular pedicle resulting from traction by the abnormally mobile or prolapsed kidney; and (b) compression or constriction of the vascular pedicle as a result of renal torsion, ureteral kinks, fibrotic bands, adhesions, or aberrant vessels, which are the usual pathologic conditions associated with nephroptosis. The effect of these vascular changes upon the intrinsic circulation of the kidney may take place long before the intrarenal circulation changes caused by the hydronephrotic atrophy are manifested. It is only within the past two years that methods have been devised which enable us to determine the extent or effect of these primary vascular changes of nephroptosis upon the renal circulation and function. Smith and his colleagues have described an inulin clearance test which serves to determine the glomerular filtrate rate, while White and Rolf utilized a diodrast clearance test for the determination of the total renal plasma flow.

McCanu and Romansky have recently studied the relation of orthostatic hypertension to nephroptosis by means of erect and recumbent pyelograms and by comparing the effect of posture on the blood pressure, on the glomerular filtration rate, and on renal blood flow. They found that in some instances of nephroptosis the erect posture may cause an orthostatic hypertension with diminution of total renal blood flow and relative constancy of glomerular filtration. They explained these findings; viz., (1) erect posture causes some slight interference with the afferent blood supply of the kidney which leads to the production of renin, and (2) the renin in turn acts to constrict the vasa efferentia in both kidneys which results in a decrease in the total renal blood flow without any appreciable effect on the glomerular filtration rate. They reported 5 cases of orthostatic hypertension associated with nephroptosis but strongly emphasized the fact that not all cases of nephroptosis are accompanied by hypertension. Only one patient, a female 56 years of age, who had been treated for benign hypertension for years and had entered a malignant phase of the disease, was subjected to operation after urologic study revealed a bilateral nephroptosis with a moderate right hydronephrosis. At operation a sclerotic aberrant vessel leading to the upper pole of the right kidney was ligated and a nephropexy was performed. Following the operation, the blood pressure remained elevated (above 200 mm.), but the episodes of cardiac, cerebral, and ocular symptoms disappeared and there was a marked symptomatic improvement. The authors urged that all hypertensive patients should be studied for the effect of posture upon the blood pressure and that those patients exhibiting orthostatic hypertension should receive pyelographic study and appropriate treatment, surgical or otherwise, if nephroptosis is disclosed.

I have observed 2 cases of hypertension associated with nephroptosis which are not included in Table I or II. The first patient was a female 19 years of age with a preoperative hypertension of 150/84, and following denervation of the renal pedicle and a Kelly nephropexy, the blood pressure fell to 130/80. The second patient was a female, 46 years of age, who had a preoperative hypertension of 156/86, and following pyelolithotomy and nephropexy, the blood pressure fell to 120/80 during her hospitalization. Unfortunately, a follow-up study of the blood pressure in both cases was not possible, as the patients left the city and could not be traced.

Ritch had previously reported excellent results from the standpoint of improvement in renal function and reduction in blood pressure which were achieved by establishing good urinary drainage by ureteral dilatation in a case of hydronephrosis with ptosis and obstruction at the ureteropelvic junction and by nephropexy in another case. Schroeder and Steele observed 2 cases of unilateral hydronephrosis associated with ptosis in their series of 71 cases of essential hypertension. Schroeder and Fish have described 2 cases of hydronephrosis with arterial hypertension treated by nephrectomy. An excellent result was obtained in their Case 6, in which a marked left hydronephrosis and hydroureter due to a stricture of the ureterovesical junction was removed despite the presence of a slight hydronephrosis and ptosis of the left kidney. Slight improvement manifested by a considerable reduction in blood pressure for six months was obtained in the patient in their Case 3, who had a nephrectomy for an advanced left hydronephrosis and a moderate hydronephrosis with ptosis on the right side.

*(To be concluded in the July issue. The references will accompany the last section.)*

# Review of Recent Meetings

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## REPORT OF THE MEETING OF THE PACIFIC COAST SURGICAL ASSOCIATION, LOS ANGELES, CALIF.,

FEB. 19-22, 1941

H. H. SEARLS, M.D., SAN FRANCISCO, CALIF.

**President's Address: The Surgical Aspects of Chronic Duodenal Ulcer, Charles T. Sturgeon, Los Angeles.**—Sturgeon outlined the indications for surgical treatment and the different operative procedures in use. He recommended partial gastrectomy with partial duodenectomy as the operation of choice when the age and physical condition of the patient permit. He concluded with a warning that all patients should be kept under medical supervision for a long time after operation. An extensive list of references was appended.

**A Family With Hemolytic Icterus, H. H. Searls, San Francisco.**—Searls described a family in which four patients with congenital hemolytic icterus were encountered, from three of whom he had removed the spleen. He discussed the literature and presented the clinical picture of the disease. Case reports were included.

The paper was discussed by J. H. Woolsey, Woodland, Calif., who had observed that pregnancy in the presence of this disease was dangerous and had terminated fatally in several instances. He suggested that the surgical demonstration of deeply pigmented gallstones should suggest a study of the blood picture of the patient in order to rule out the possibility of hemolytic icterus. H. Glenn Bell, San Francisco, discussed the paper and reported a family of five persons who had the disease.

**Back Disabilities Due to Strain of the Multifidus Muscle—Treated by Novocain Injections, William K. Livingston, Portland, Ore.**—Livingston noted that in some cases of low back disability the essential lesion may be small and local, while the syndrome of widespread muscle spasm, neuritis, and so forth may result from secondary reflex disturbances. He pointed out that a very common location of such local lesions is the multifidus muscle in the region of the sacrum. If the "trigger point" can be located, novocain solution injected at this point may relieve the whole vicious cycle of reflexes.

Edgar L. Gilcreest, San Francisco, in discussion, observed that the cause of low back pain is often difficult to find. Stretching and manipulation gave relief in a large percentage of his cases, but he expressed gratitude that Livingston offered a new therapeutic measure for the treatment of this syndrome. E. W. Rokey, Portland, testified that Livingston had relieved him of a very serious pain in the back, which had followed a fall. A. R. Kilgore, San Francisco, reported a similar case. Frederick Reichert, San Francisco, emphasized the importance of accurately locating trigger points. LeRoy Abbott, San Francisco, reported having seen Lawrence Mayers, of Chicago, relieve pain by injection along

the spine with a special solution which he calls "astroform." Homer Dudley, Seattle, Wash., warned that the pain may recur after such treatment.

**Injuries to Ligaments of the Knee, LeRoy C. Abbott, John Saunders, and Carl Anderson, San Francisco.**—In this article the authors stressed the importance of early and thorough examination of all injuries to the knee in order to establish promptly an accurate anatomic diagnosis and thereby apply the appropriate method of treatment. They described certain methods of examination of great practical value in arriving at the correct diagnosis and discussed the mechanism of injury to the ligament and the clinical findings in each type of injury. An outline of treatment concluded the paper.

**Harold Hitchcock, Oakland, Calif.,** in discussion urged, for minor injuries, early strapping and exercises for the quadriceps. He pointed out that immobilization results in such a weakening of the quadriceps that the disability is considerably aggravated. Aspiration of the joint is an important part of the treatment. In the more serious injuries of the knee, examination should be done under anesthesia. **John C. Wilson, Los Angeles,** considered the authors' physiological and anatomical discussions of the knee joint to be of great practical value. In closing, Abbott again emphasized that early operation is of very great importance in severely damaged joints which show marked rocking and spread of the joint, by x-ray examination.

**The Urological Complications of Carcinoma of the Rectum, Thomas F. Mullen and Paul Lestrohan, San Francisco.**—The authors observed that symptoms related to the urinary tract are found in a high percentage of patients having cancer of the rectum and urged more specific attention to these symptoms before operation. They questioned the advisability of the routine use of the retention catheter and expressed the belief that if it is used it should always be accompanied by tidal irrigation. They recommended preservation of the pelvic splanchnic distribution to the urinary and sexual apparatus, whenever possible, by special attention to the anatomy of the posterior pelvic fascial planes. An effort should be made to prevent prolapse of the bladder into the posterior wound, and every attention given to the prevention of postoperative cystitis.

**Frank Hinman, San Francisco,** discussed this paper, concluding that these patients should have a complete urological study before operation, anatomical dissection at operation, and that the problem of urological complications should have careful attention both before and after operation. **E. Eric Larson, Los Angeles,** recommended the use of chemotherapy as a prophylactic preoperative measure for the prevention of urinary infection and urged that the surgeon obtain the co-operation of a competent urologist before, during, and after operation.

**Acute Pancreatitis, George K. Rhodes, San Francisco.**—Rhodes discussed the etiology, clinical picture, and differential diagnosis of this disease. The blood amylase determination was considered to be of great aid in differential diagnosis. He recommended conservative treatment during the acute stage whenever possible.

**E. Eric Larson, Los Angeles,** in discussion, described the serum amylase test and again emphasized its value as an aid to the diagnosis of acute pancreatitis. **H. Glenn Bell, San Francisco,** warned that, as a general policy, too much weight should not be placed on a laboratory procedure and that there was a possibility of missing other acute conditions in the abdomen by not operating.

**The Problem of the Common Duct Stone, J. H. Woolsey, Woodland, Calif.**—Woolsey discussed the etiology and diagnosis and emphasized the value of variations in the ieterus index at the time of colic, the rise going from 8 to 16 and even to 33 per cent. In all of his cases in which this variation was noted, stones

were present in the common duct. He then discussed the treatment and urged that, in doubtful cases, exploration should be done.

**Wayland A. Morrison**, Los Angeles, in discussing Woolsey's paper, said that he was in agreement with Woolsey in urging more frequent exploration of the common duct. **George K. Rhodes**, San Francisco, recommended the use of vitamin K in jaundiced patients and the making of cholangiograms at the table. He emphasized the importance of using considerable carbohydrate infusion before operation.

**Secondary Operations on the Biliary System After Cholecystectomy**, **Robert D. Forbes**, Seattle.—The author discussed the hazards of the approach in operating for the second time. He named the indications for this operation (the most common being some form of obstructive jaundice) and then discussed the differential diagnosis, finally reviewing a series of records of fifteen patients upon whom operations had been performed for biliary disease following cholecystectomy. The author urged a more frequent exploration of the common duct at the time of performing cholecystectomy.

**Verne C. Hunt**, Los Angeles, said that, in his opinion, the common duct should be opened much more frequently than is the present practice in performing cholecystectomy. He felt that this would be an important prophylactic move against the development of the type of cases described by Forbes.

**Aseptic Technic for Resection of the Stomach**, **Emile F. Holman**, San Francisco.—Holman presented a motion picture in illustration of this subject. By using Payr clamps and a cautery, he was able to do a partial gastrectomy under aseptic conditions, no viscus being opened at any time. There was no discussion.

**An Instrument for Retraction of Viscera During Peritoneoscopy**, **Samuel Robinson** and **L. Gordon Fiske**, Santa Barbara, Calif.—The authors described an instrument which, at the time of peritoneoscopy, may be inserted through a separate puncture wound into the abdomen. It consists of a cannula or tube, through which a web-footed retractor is inserted into the abdomen. The web foot consists of three blades which open fanwise when a thread is turned at the proximal end of the shaft. These three blades are covered with a latex seamless rubber bag, shaped like a tennis racket. The neck of the bag is tied to the shaft of the retractor with silk thread. Under the observation of the peritoneoscopist, looking through his peritoneoscope, the retractor is used to move about the different viscerae to give a better view of what is being seen.

**John C. Ruddock**, Los Angeles, who has had a very extensive experience with peritoneoscopy, stated in discussion that he would welcome this instrument as an adjunct to his work. He then went on to classify the work of the peritoneoscope as to what it would show, the type of patient to be selected for its use, and so forth. **Harold Brunn**, San Francisco, although admitting the value of the peritoneoscope, pointed out that errors of interpretation made in using it might be extremely dangerous or even fatal.

**Hyperparathyroidism**, **H. S. Chapman**, Stockton, Calif.—After a complete discussion of the literature and a careful clinical description of the disease, the author presented his own case.

**P. K. Gilman**, San Francisco, in discussion, reported two cases from the Stanford Hospital. **H. H. Searls**, San Francisco, discussed the laboratory findings, anatomy, and operative procedures in these cases.

**New Treatment for Residual and Progressive Postoperative Exophthalmos**, **Brien King**, Seattle.—King presented a preliminary report in which he stated that x-ray therapy to the general region of the front of the neck had resulted in the

regression of postoperative exophthalmos. Admitting the method to be empirical, he nevertheless hoped that others would follow his lead so that a sufficient number of cases could be observed to assay its value.

Howard C. Naffziger, San Francisco, in discussion hoped that accurate observations with the exophthalmometer would be performed and that many basal metabolic rates would be determined in the further investigation of this method of treatment.

**Carcinoma of the Cervical Stump, Raymond E. Watkins, Portland.**—Careful pre-operative study of patients requiring hysterectomy for seemingly benign conditions would reveal associated carcinoma in most instances when cancer is associated. The prognosis in true carcinoma of the stump is much brighter than is generally recognized. Irradiation of cervical stump cancer is the method of choice. The author performs total hysterectomy for benign tumors if the patient has a diseased cervix, because he feels that cervical lacerations, endocervicitis, cystic degeneration, and extensive erosion are definitely predisposing factors in the production of carcinoma. If total hysterectomy is contraindicated because of the condition of the patient, the cervix can be treated from below at a later time. He believes that leaving the normal cervix subjects the patient to little risk. Removal of the endocervical mucous membrane is of limited value. A careful preliminary study of every patient who is to be subjected to hysterectomy should be done.

A. B. Kilgore, San Francisco, in discussing this paper, recommended subtotal hysterectomy in young women with a healthy cervix, but in older women in the cancer age, and particularly in those whose cervices are diseased, total hysterectomy should be performed.

**An Appliance for Colostomy Control, O. F. Lamson, Seattle.**—The author demonstrated a mechanism he devised for the control of a colostomy. A small, thin-walled rubber bag could be inflated after being placed within the colostomy and attached by a hollow tube to a plastic disk which rested on the external opening. The thickness of the abdominal wall was first measured in order to have the proper length of tubing. This tubing serves the purpose of holding the bag to the disk on the abdominal wall and also permits the passage of air into the bag when it is being inflated. The author stated that it had been used successfully in a number of cases. A general discussion indicated that the members of the Association felt that this apparatus might have a distinct place in the control of a colostomy.

## Book Reviews

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**The Endocrine Function of Iodine.** By William T. Salter. Cambridge, 1940. Harvard University Press. Pp. 351, with 38 illustrations.

This monograph brings together between covers for the first time a comprehensive account of the chemical, physiologic, and clinical information relating to the metabolism and function of iodine compounds in the animal body. It is written from the background of extensive experimental experience in the field and is of unquestionable value to anyone interested in thyroid function in health or disease. The author has reviewed the older as well as the most recent literature, covering 588 references, and has adequately described the results of studies of iodine balance, of tracer experiments with radio iodine, of estimations of circulating iodine in health and disease, and of other observations. The style is lucid and readable.

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**A Method of Anatomy. Descriptive and Deductive.** By J. C. Boileau Grant, M.C., M.B., Ch.B., F.R.C.S. (Edin.). Professor of Anatomy in the University of Toronto. Ed. 2, Baltimore, 1940, The Williams and Wilkins Co. \$6.

Medical knowledge is increasing much more rapidly than is the power of the human mind to learn and retain the vast amount of scientific facts before us. Anatomy, pathology, physiology, and therapeutics only a few years ago were the mainstays of the study of medicine, but now the new discoveries in biochemistry, chemotherapy, and the extreme development of specialties make it necessary that the time spent on the old fundamentals be shortened that the new essential information be taught. This necessitates short cuts by new methods of teaching and study of anatomy since the student of today now has one-fourth to one-third the number of hours to devote to this subject as compared to students of twenty to thirty years ago. It is with considerable misgiving that we accept this new order, though we realize the necessity of the change. *A Method of Anatomy* is an experiment in teaching anatomy by a short method which should be given a trial. One cannot believe it possible for one to acquire extensive anatomical knowledge without more time and the older methods of systematic dissection. Still a good working knowledge of the subject should result from a study of this book and we wait with interest the results of its more extensive use in medical schools. The coordinate presentation of physical facts and functions of the anatomical parts with simple illustrations is impressive and should help the student to retain his anatomy.

The second edition of this unique book differs from the first in the addition of a section on general anatomy and the insertion of more than 100 new figures. The new figures are line drawings of excellent quality depicting actual dissections with great clarity and accuracy. Most of them are of half-page size and completely labeled. The section on general anatomy covers many of the more important facts of systematic anatomy with telegraphic brevity but is nevertheless very readable

and enlivened by considerable practical physiology. The brain, and the endocrine glands as a system are not considered. These are regrettable omissions since their addition would furnish the beginning student with an excellent sketch of the entire scope of his anatomical training. Numerous minor improvements have been made throughout the original text, but with the exceptions noted above, the second edition differs little from the first. Missing is a list of references that would enable the reader to locate the work of the numerous authors mentioned throughout the book. Professor Grant's book remains what the title suggests, a method of presenting gross anatomy to the beginning student. As such it offers a distinct and admirable challenge to teachers of anatomy to present their subject in an equally lucid manner and to the student a refreshing relief from dry bones and lifeless muscles; however, it does not eliminate the need for each medical student to possess one of the larger standard textbooks of anatomy, both for his anatomical courses and as a reference in subsequent years. Other than a book for medical students we believe it will be of good value for the graduate who wishes to review his anatomy. He will find the subject presented in a manner that will make anatomical study a pleasure.

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**The Injured Back and Its Treatment.** Edited by John D. Ellis, M.D. Cloth. Pp. 377, Springfield, Ill., 1940, Charles C Thomas, Publisher. \$5.50.

This timely book of convenient size is beautifully printed and well illustrated. It is alone in its field and it presents a compilation of present-day information which should make it a useful addition to the libraries of all practitioners who are called upon to diagnose and treat painful backs. The contents are divided into nine chapters, of which three are by the editor and the remaining six by seven contributing authors. Ellis presents a most valuable chapter of sixty pages on "The Routine Examination of the Injured Back," giving a clear discussion and differentiation of the injuries of the lower back and related conditions. Professor Sir Arthur Keith has written the introductory chapter and discusses the posture of man from the viewpoint of comparative anatomy and physiology. Conwell presents compression fractures of vertebral bodies and Davis and Haven discuss neurosurgic aspects of back injuries. Ghormley discusses the diagnosis and treatment of conditions involving the articular facets and Osgood gives us an inspiring chapter on faulty body mechanics and posture in relation to both the prevention and care of back injuries. A very valuable and instructive chapter has been contributed by Davis on backache as a symptom of visceral disease and reflex pains in the back which may be mistakenly considered as due to injury. This chapter should be valuable to those who are called upon to treat or testify where objective symptoms are absent and the injury is questionable.

A chapter presenting modern methods of first aid and transportation of injured backs would have been welcome, and it is to be hoped that the present-day standardized procedures will appear in the next edition. There is considerable valuable information on x-ray diagnostic procedures distributed through the book, but it is inadequately indexed and hard to find. A chapter in the next edition devoted to directions for the taking of diagnostic x-rays of the different parts of the spine would furnish a much needed addition, because this book will be useful in the more remote sections of the English-speaking world as well as in the large medical centers.

**Clinical Pellagra.** By Seale Harris, M.D., Professor Emeritus of Medicine, University of Alabama, and Seale Harris, Jr., M.D., Formerly Assistant Professor of Medicine, Vanderbilt University. Pp. 494, with 70 illustrations, including 4 in color. St. Louis, 1941, the C. V. Mosby Company. \$7.

In view of the striking and rapid advances in the field of nutritional diseases, Seale Harris' *Clinical Pellagra* is especially welcome to the clinician.

Written in admirable, conversational style, the book is replete with the salient features and cogent factual information of students of pellagra the world over; in addition, one derives benefit from the mature, keen analysis and interpretations of a number of leading experts in the field of nutrition. Among the many salient features of the book are included a fascinating and extraordinarily complete history of the disease, an interpretation of the available theories of the etiology of pellagra in the light of modern investigative advances, special sections by Ruffin, Smith, Sydenstricker, Porter, Higginbotham, and others, dealing with special problems in pellagra, lending immensely to the value of the text. The rationale of the treatment of the pellagrous patient is so clearly indicated that the veriest tyro in the field of nutritional problems may easily master the fundamental principles of the management of pellagra.

The book consists of six sections, dealing with the history of pellagra, its etiology, current clinical investigations, symptomatology, diagnosis and prognosis, prophylaxis, and treatment. Numerous excellent plates illustrate the clinical manifestations of the disease. An extensive bibliography includes virtually every significant contribution to the study of pellagra. Certainly the book constitutes the most concise, well-authenticated treatise on pellagra extant today.

Dr. Harris has succeeded in writing "a factual treatise on pellagra, in which the various phases of the subject are discussed, including summaries of the most important contributions by those who may be regarded as authorities on the subject."

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**Endocrine Gynecology.** By E. C. Hamblen. Cloth. Pp. 453, with 160 illustrations. Springfield, Ill., Charles C Thomas, Publisher. \$5.50.

The author has done a magnificent task with a subject that is changing rapidly as a result of the relatively enormous amount of investigative work that is being done in the field of gynecologic endocrinology. The style is easy, and the clearly written text is profusely illustrated. The color plates have been beautifully prepared, and the photomicrographs are good, being adequate to complete the descriptions of each disease considered.

One of the outstanding qualities of the book is the clear thinking along lines of histopathologic diagnosis with a resultant logical course in treatment. The terminology is accurate, and such conditions as menstruation and anovulatory bleeding are definitely catalogued, with vague terms as functional bleeding avoided. The psychic influence on the behavior of the glands of internal secretion has never before been as clearly described nor emphasized as much.

Though the author admittedly has written this text for the physician doing general practice, the subject is thoroughly covered and the references are complete, making the book suitable for many other physicians, especially those doing gynecology.

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